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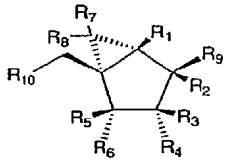

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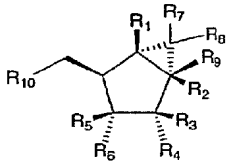

(II)

(57) Abstract: The invention provides a compound of formula (I) and (II), or a salt or prodrug thereof, as described herein, as well as pharmaceutical compositions comprising the compounds, and therapeutic methods comprising administering the compounds. The compounds have anti-viral properties and are useful for treating viral infections (e.g. HCV) in animals (e.g. humans).

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BICYCLO(3.1.0)HEXANE DERIVATIVES AS ANTIVIRAL COMPOUNDS

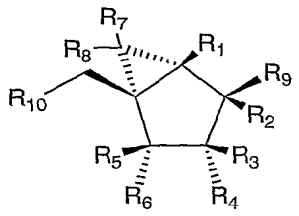
BACKGROUND OF THE INVENTION

Hepatitis C (HCV) is the most comon blood-born infection in the United States, where about 35,000 new cases are estimeted to occur each year. There is currently a need for compounds, compositions, and methods that are useful for treating viral infections such as HCV.

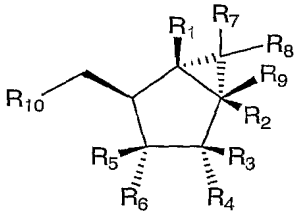
SUMMARY OF THE INVENTION

The present invention provides compounds that inhibit one or more viral proteases. Accordingly, the compounds may be useful for treating viruses, such as HCV.

In one embodiment the invention provides a compound of the invention, which is a compound of formula I or II:



(I)



(II)

wherein:

R_1 is H, halo, OR_a, SR_a, or NR_bR_c;

R_2 is H, halo, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, or $(C_2\text{-}C_6)$alkynyl;

R_3 is H, halo, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, or $(C_2\text{-}C_6)$alkynyl; and R_4 is H, halo, azido, cyano, nitro, OR_a, SR_a, NR_bR_c, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, or $(C_2\text{-}C_6)$alkynyl; or R_3 and R_4 taken together are =O, $=NR_d$, $=CR_fR_g$; or R_3 and R_4 taken together with the carbon atom to which they are attached form a 3-7 membered carbocyclic ring wherein one carbon atom can optionally be replaced with -O-, -S-, or $-NR_a$-;

R_5 is H, halo, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, or $(C_2\text{-}C_6)$alkynyl; and R_6 is H, halo, azido, cyano, nitro, OR_a, SR_a, NR_bR_c, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, or

(C_2-C_6)alkynyl; or R_5 and R_6 taken together are =O, =NR_d, =CR_fR_g; or R_5 and R_6 taken together with the carbon atom to which they are attached form a 3-7 membered carbocyclic ring wherein one carbon atom can optionally be replaced with -O-, -S-, or –NR_a-;

R_7 and R_8 are each independently H or halo;

R_9 is a nucleoside base;

R_{10} is OH, -OP(=O)$(OH)_2$, -OP(=O)(OH)-P(=O)$(OH)_2$, -OP(=O)(OH)-P(=O)(OH)-P(=O)$(OH)_2$, or a phosphonate;

each R_a is independently H, (C_1-C_6)alkyl, or (C_1-C_6)alkanoyl;

each R_b and R_c is independently H, (C_1-C_6)alkyl, or (C_1-C_6)alkanoyl;

each R_d is independently H, (C_1-C_6)alkyl, or OH;

each R_e is independently H or (C_1-C_6)alkyl; and

each R_f and R_g is independently H, (C_1-C_6)alkyl, or halo;

wherein each (C_1-C_6)alkyl, (C_2-C_6)alkenyl, or (C_2-C_6)alkynyl of R_2-R_6 and R_a-R_g is optionally substituted with one or more halo, hydroxy, or (C_1-C_6)alkoxy;

or a pharmaceutically acceptable salt or prodrug thereof.

The invention also provides a pharmaceutical composition comprising an effective amount of a compound of the invention, or a pharmaceutically acceptable salt or prodrug thereof, and a pharmaceutically acceptable excipient.

The invention also provides metabolites of compounds of the invention, as well as salts thereof.

The invention also provides a method of inhibiting a viral infection in an animal (e.g. a mammal), comprising administering an effective amount a compound of the invention, or a pharmaceutically acceptable salt or prodrug thereof, to the animal.

The invention also provides a compound of the invention for use in medical therapy (preferably for use in treating a viral infection in an animal), as well as the use of a compound of the invention for the manufacture of a medicament useful for the treatment of a viral infection in an animal (e.g. a mammal).

The invention also provides processes and novel intermediates disclosed herein which are useful for preparing compounds of the invention. Some of the

compounds of the invention are useful to prepare other compounds of the invention.

In another embodiment the invention provides a method for inhibiting a viral infection in a sample comprising treating a sample suspected of containing a virus, with a compound of the invention, or a pharmaceutically acceptable salt or prodrug thereof.

BRIEF DESCRIPTION OF THE FIGURES

Figures 1-4 illustrate synthetic processes and intermediates that can be used to prepare compounds of the invention.

DETAILED DESCRIPTION OF THE INVENTION

Unless stated otherwise, the following terms and phrases as used herein are intended to have the following meanings:

When tradenames are used herein, applicants intend to independently include the tradename product and the active pharmaceutical ingredient(s) of the tradename product.

Alkyl, alkoxy, alkenyl, alkynyl, etc. denote both straight and branched groups; but reference to an individual radical such as propyl embraces only the straight chain radical, a branched chain isomer such as isopropyl being specifically referred to.

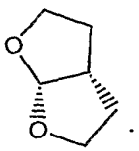
"Aryl" means a monovalent aromatic hydrocarbon radical of 6-20 carbon atoms derived by the removal of one hydrogen atom from a single carbon atom of a parent aromatic ring system. Typical aryl groups include, but are not limited to, radicals derived from benzene, substituted benzene, naphthalene, anthracene, biphenyl, and the like.

"Carbocycle" refers to a saturated, unsaturated or aromatic ring having 3 to 7 carbon atoms as a monocycle, 7 to 12 carbon atoms as a bicycle, and up to about 20 carbon atoms as a polycycle. Monocyclic carbocycles have 3 to 6 ring atoms, still more typically 5 or 6 ring atoms. Bicyclic carbocycles have 7 to 12 ring atoms, *e.g.*, arranged as a bicyclo [4,5], [5,5], [5,6] or [6,6] system, or 9 or 10 ring atoms arranged as a bicyclo [5,6] or [6,6] system. Examples of monocyclic carbocycles include cyclopropyl, cyclobutyl, cyclopentyl, 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, cyclohexyl, 1-

cyclohex-1-enyl, 1-cyclohex-2-enyl, 1-cyclohex-3-enyl, phenyl, spiryl and naphthyl.

"Heterocycle" as used herein includes, by way of example and not limitation, those heterocycles described in Paquette, Leo A.; Principles of Modern Heterocyclic Chemistry (W.A. Benjamin, New York, 1968), particularly Chapters 1, 3, 4, 6, 7, and 9; The Chemistry of Heterocyclic Compounds, A Series of Monographs" (John Wiley & Sons, New York, 1950 to present), in particular Volumes 13, 14, 16, 19, and 28; and *J. Am. Chem. Soc.* (1960) 82:5566. In one specific embodiment of the invention "heterocycle" includes a "carbocycle" as defined herein, wherein one or more (*e.g.*, 1, 2, 3, or 4) carbon atoms have been replaced with a heteroatom (*e.g.*, O, N, or S).

Examples of heterocycles include, by way of example and not limitation, pyridyl, dihydroypyridyl, tetrahydropyridyl (piperidyl), thiazolyl, tetrahydrothiophenyl, sulfur oxidized tetrahydrothiophenyl, pyrimidinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, tetrazolyl, benzofuranyl, thianaphthalenyl, indolyl, indolenyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, 4-piperidonyl, pyrrolidinyl, 2-pyrrolidonyl, pyrrolinyl, tetrahydrofuranyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, octahydroisoquinolinyl, azocinyl, triazinyl, 6H-1,2,5-thiadiazinyl, 2H,6H-1,5,2-dithiazinyl, thienyl, thianthrenyl, pyranyl, isobenzofuranyl, chromenyl, xanthenyl, phenoxathinyl, 2H-pyrrolyl, isothiazolyl, isoxazolyl, pyrazinyl, pyridazinyl, indolizinyl, isoindolyl, 3H-indolyl, 1H-indazoly, purinyl, 4H-quinolizinyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, 4aH-carbazolyl, carbazolyl, β-carbolinyl, phenanthridinyl, acridinyl, pyrimidinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, furazanyl, phenoxazinyl, isochromanyl, chromanyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, piperazinyl, indolinyl, isoindolinyl, quinuclidinyl, morpholinyl, oxazolidinyl, benzotriazolyl, benzisoxazolyl, oxindolyl, benzoxazolinyl, isatinoyl, and bis-tetrahydrofuranyl:



By way of example and not limitation, carbon bonded heterocycles are bonded at position 2, 3, 4, 5, or 6 of a pyridine, position 3, 4, 5, or 6 of a pyridazine, position 2, 4, 5, or 6 of a pyrimidine, position 2, 3, 5, or 6 of a pyrazine, position 2, 3, 4, or 5 of a furan, tetrahydrofuran, thiofuran, thiophene, pyrrole or tetrahydropyrrole, position 2, 4, or 5 of an oxazole, imidazole or thiazole, position 3, 4, or 5 of an isoxazole, pyrazole, or isothiazole, position 2 or 3 of an aziridine, position 2, 3, or 4 of an azetidine, position 2, 3, 4, 5, 6, 7, or 8 of a quinoline or position 1, 3, 4, 5, 6, 7, or 8 of an isoquinoline. Still more typically, carbon bonded heterocycles include 2-pyridyl, 3-pyridyl, 4-pyridyl, 5-pyridyl, 6-pyridyl, 3-pyridazinyl, 4-pyridazinyl, 5-pyridazinyl, 6-pyridazinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl, 2-pyrazinyl, 3-pyrazinyl, 5-pyrazinyl, 6-pyrazinyl, 2-thiazolyl, 4-thiazolyl, or 5-thiazolyl.

By way of example and not limitation, nitrogen bonded heterocycles are bonded at position 1 of an aziridine, azetidine, pyrrole, pyrrolidine, 2-pyrroline, 3-pyrroline, imidazole, imidazolidine, 2-imidazoline, 3-imidazoline, pyrazole, pyrazoline, 2-pyrazoline, 3-pyrazoline, piperidine, piperazine, indole, indoline, 1H-indazole, position 2 of a isoindole, or isoindoline, position 4 of a morpholine, and position 9 of a carbazole, or β-carboline. Still more typically, nitrogen bonded heterocycles include 1-aziridyl, 1-azetedyl, 1-pyrrolyl, 1-imidazolyl, 1-pyrazolyl, and 1-piperidinyl.

Heterocycle encompasses "heteroaryl," which includes a radical attached via a ring carbon of a monocyclic aromatic ring containing five or six ring atoms consisting of carbon and one to four heteroatoms each selected from the group consisting of non-peroxide oxygen, sulfur, and N(X) wherein X is absent or is H, O, $(C_1\text{-}C_4)$alkyl, phenyl or benzyl, as well as a radical of an ortho-fused bicyclic heterocycle of about eight to ten ring atoms derived therefrom, particularly a benz-derivative or one derived by fusing a propylene, trimethylene, or tetramethylene diradical thereto.

The term "substituted heterocycle" includes heterocycles as described herein that are substituted with one or more (e.g. 1, 2, 3, or 4) substituents selected from $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkylthio, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkanoyl, $(C_1\text{-}C_6)$alkanoyloxy, $(C_1\text{-}C_6)$alkoxycarbonyl, oxo, $NR_{xx}R_{yy}$ $-C(=O)NR_{xx}R_{yy}$, cyano, halo, hydroxy, nitro, carboxy, $(C_3\text{-}C_8)$cycloalkyl, $(C_3\text{-}C_8)$cycloalkoxy,

guanidino, trifluoromethoxy, mercapto, or trifluoromethyl; wherein R_{xx} and R_{yy} are each independently *H*, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkanoyl, or aryl$(C_1\text{-}C_6)$alkyl.

The terms "phosphonate" and "phosphonate group" include functional groups or moieties within a molecule that comprises a phosphorous that is 1) single-bonded to a carbon, 2) double-bonded to a heteroatom, 3) single-bonded to a heteroatom, and 4) single-bonded to another heteroatom, wherein each heteroatom can be the same or different. The terms "phosphonate" and "phosphonate group" also include functional groups or moieties that comprise a phosphorous in the same oxidation state as the phosphorous described above, as well as functional groups or moieties that comprise a prodrug moiety that can separate from a compound so that the compound retains a phosphorous having the characteristics described above. For example, the terms "phosphonate" and "phosphonate group" include phosphonic acid, phosphonic monoester, phosphonic diester, phosphonamidate, and phosphonthioate functional groups. In one specific embodiment of the invention, the terms "phosphonate" and "phosphonate group" include functional groups or moieties within a molecule that comprises a phosphorous that is 1) single-bonded to a carbon, 2) double-bonded to an oxygen, 3) single-bonded to an oxygen, and 4) single-bonded to another oxygen, as well as functional groups or moieties that comprise a prodrug moiety that can separate from a compound so that the compound retains a phosphorous having such characteristics. In another specific embodiment of the invention, the terms "phosphonate" and "phosphonate group" include functional groups or moieties within a molecule that comprises a phosphorous that is 1) single-bonded to a carbon, 2) double-bonded to an oxygen, 3) single-bonded to an oxygen or nitrogen, and 4) single-bonded to another oxygen or nitrogen, as well as functional groups or moieties that comprise a prodrug moiety that can separate from a compound so that the compound retains a phosphorous having such characteriatics.

The term "treatment" or "treating," to the extent it relates to a disease or condition includes preventing the disease or condition from occurring, inhibiting the disease or condition, eliminating the disease or condition, and/or relieving one or more symptoms of the disease or condition.

Prodrugs

The term "prodrug" as used herein refers to any compound that when administered to a biological system generates the drug substance, *i.e.* active ingredient, as a result of spontaneous chemical reaction(s), enzyme catalyzed chemical reaction(s), photolysis, and/or metabolic chemical reaction(s). A prodrug is thus a covalently modified analog or latent form of a therapeutically-active compound.

"Prodrug moiety" refers to a labile functional group which separates from the active inhibitory compound during metabolism, systemically, inside a cell, by hydrolysis, enzymatic cleavage, or by some other process (Bundgaard, Hans, "Design and Application of Prodrugs" in A Textbook of Drug Design and Development (1991), P. Krogsgaard-Larsen and H. Bundgaard, Eds. Harwood Academic Publishers, pp. 113-191). Enzymes which are capable of an enzymatic activation mechanism with a phosphate prodrug of the invention include, but are not limited to, amidases, esterases, microbial enzymes, phospholipases, cholinesterases, and phosphases. Prodrug moieties can serve to modulate (e.g. enhanse) solubility, absorption, lipophilicity, drug delivery, bioavailability, and efficacy.

Exemplary prodrug moieties include the hydrolytically sensitive or labile acyloxymethyl esters $-CH_2OC(=O)R^x$ and acyloxymethyl carbonates $-CH_2OC(=O)OR^x$ where R^x is (C_1-C_6)alkyl, (C_1-C_6)substituted alkyl, C_6-C_{20} aryl or C_6-C_{20} substituted aryl. The acyloxyalkyl ester was first used as a prodrug strategy for carboxylic acids and then applied to phosphates and phosphonates by Farquhar et al. (1983) *J. Pharm. Sci.* 72: 324; also US Patent Nos. 4816570, 4968788, 5663159 and 5792756. Subsequently, the acyloxyalkyl ester was used to deliver phosphonic acids across cell membranes and to enhance oral bioavailability. A close variant of the acyloxyalkyl ester, the alkoxycarbonyloxyalkyl ester (carbonate), may also enhance oral bioavailability of a compound of the invention. An exemplary acyloxymethyl ester is pivaloyloxymethoxy, (POM) $-CH_2OC(=O)C(CH_3)_3$. An exemplary acyloxymethyl carbonate prodrug moiety is pivaloyloxymethylcarbonate (POC) $-CH_2OC(=O)OC(CH_3)_3$.

Aryl esters of phosphorus groups, especially phenyl esters, are reported

to enhance oral bioavailability (De Lombaert et al. (1994) *J. Med. Chem.* 37: 498). Phenyl esters containing a carboxylic ester ortho to the phosphate have also been described (Khamnei and Torrence, (1996) *J. Med. Chem.* 39:4109-4115). Benzyl esters are reported to generate the parent phosphonic acid. In some cases, substituents at the *ortho*-or *para*-position may accelerate the hydrolysis. Benzyl analogs with an acylated phenol or an alkylated phenol may generate the phenolic compound through the action of enzymes, *e.g.*, esterases, oxidases, etc., which in turn undergoes cleavage at the benzylic C–O bond to generate the phosphoric acid and a quinone methide compound. Examples of this class of prodrugs are described by Mitchell et al. (1992) *J. Chem. Soc. Perkin Trans. II* 2345; and Glazier WO 91/19721. Still other benzylic prodrugs have been described containing a carboxylic ester-containing group attached to the benzylic methylene (Glazier WO 91/19721).

Thio-containing prodrugs are reported to be useful for the intracellular delivery of phosphorous containing drugs. Certain of these proesters contain an ethylthio group in which the thiol group is either esterified with an acyl group or combined with another thiol group to form a disulfide. Deesterification or reduction of the disulfide generates the free thio intermediate, which subsequently breaks down to the phosphoric acid and an episulfide (Puech et al. (1993) *Antiviral Res.*, 22: 155-174; Benzaria et al. (1996) *J. Med. Chem.* 39: 4958).

Prodrug moities that can be incorporated into compounds of the invention include those described by Mackman, R.L. and Cihlar, Tomas, *Annual Reports in Medicinal Chemistry,* **2004**, *39*, 305-321. Other prodrug moities that can be incorporated into compounds of the invention include those described by Peyrottes et. al., *Minireviews in Medicinal Chemistry*, **2004**, *4*(4), 395-408; and Meier, Chris, *Advances in Antiviral Drug Design*, **2004**, *4*, 147-213.

Protecting Groups

In the context of the present invention, protecting groups include prodrug moieties and chemical protecting groups.

"Protecting group" refers to a moiety of a compound that masks or alters the properties of a functional group or the properties of the compound as a

whole. Chemical protecting groups and strategies for protection/deprotection are well known in the art. *See e.g.*, Protective Groups in Organic Chemistry, Theodora W. Greene, John Wiley & Sons, Inc., New York, 1991. Protecting groups are often utilized to mask the reactivity of certain functional groups and to assist in the efficiency of desired chemical reactions, *e.g.*, making and breaking chemical bonds in an ordered and planned fashion. Protection of functional groups of a compound alters other physical properties besides the reactivity of the protected functional group, such as the polarity, lipophilicity (hydrophobicity), and other properties that can be measured by common analytical tools. Chemically protected intermediates may themselves be biologically active or inactive. Protected compounds may also exhibit altered, and in some cases, optimized properties *in vitro* and *in vivo*, such as passage through cellular membranes and resistance to enzymatic degradation or sequestration. In this role, protected compounds with intended therapeutic effects are also prodrugs.

Various functional groups of the compounds of the invention may be protected. For example, protecting groups for -OH groups (whether hydroxyl, carboxylic acid, phosphonic acid, or other functions) include "ether- or ester-forming groups". Ether- or ester-forming groups are capable of functioning as chemical protecting groups in the synthetic schemes set forth herein.

A very large number of hydroxyl protecting groups and amide-forming groups and corresponding chemical cleavage reactions are described in Protective Groups in Organic Synthesis, Theodora W. Greene (John Wiley & Sons, Inc., New York, 1991, ISBN 0-471-62301-6) ("Greene"). See also Kocienski, Philip J.; Protecting Groups (Georg Thieme Verlag Stuttgart, New York, 1994). In particular Chapter 1, Protecting Groups: An Overview, pages 1-20, Chapter 2, Hydroxyl Protecting Groups, pages 21-94, Chapter 3, Diol Protecting Groups, pages 95-117, Chapter 4, Carboxyl Protecting Groups, pages 118-154, Chapter 5, Carbonyl Protecting Groups, pages 155-184. For protecting groups for carboxylic acid, phosphonic acid, phosphonate, sulfonic acid and other protecting groups for acids see Greene as set forth below. Such groups include by way of example and not limitation, esters, amides, hydrazides, and the like.

Specific Embodiments

Specific values described for radicals, substituents, and ranges, as well as specific embodiments of the invention described herein, are for illustration only; they do not exclude other defined values or other values within defined ranges.

For example, (C_1-C_6)alkyl can be methyl, ethyl, propyl, isopropyl, butyl, iso-butyl, sec-butyl, pentyl, 3-pentyl, or hexyl; (C_3-C_6)cycloalkyl can be cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl; (C_3-C_6)cycloalkyl(C_1-C_6)alkyl can be cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, 2-cyclopropylethyl, 2-cyclobutylethyl, 2-cyclopentylethyl, or 2-cyclohexylethyl; (C_1-C_6)alkoxy can be methoxy, ethoxy, propoxy, isopropoxy, butoxy, iso-butoxy, sec-butoxy, pentoxy, 3-pentoxy, or hexyloxy; (C_2-C_6)alkenyl can be vinyl, allyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 1,-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 1- hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, or 5-hexenyl; (C_2-C_6)alkynyl can be ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1- hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, or 5-hexynyl; (C_1-C_6)alkanoyl can be acetyl, propanoyl or butanoyl; hydroxy(C_1-C_6)alkyl can be hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 1-hydroxypropyl, 2-hydroxypropyl, 3-hydroxypropyl, 1-hydroxybutyl, 4-hydroxybutyl, 1-hydroxypentyl, 5-hydroxypentyl, 1-hydroxyhexyl, or 6-hydroxyhexyl; (C_1-C_6)alkoxycarbonyl can be methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, pentoxycarbonyl, or hexyloxycarbonyl; (C_1-C_6)alkylthio can be methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, pentylthio, or hexylthio; (C_2-C_6)alkanoyloxy can be acetoxy, propanoyloxy, butanoyloxy, isobutanoyloxy, pentanoyloxy, or hexanoyloxy; aryl can be phenyl, indenyl, or naphthyl; and heteroaryl can be furyl, imidazolyl, triazolyl, triazinyl, oxazoyl, isoxazoyl, thiazolyl, isothiazoyl, pyrazolyl, pyrrolyl, pyrazinyl, tetrazolyl, pyridyl, (or its N-oxide), thienyl, pyrimidinyl (or its N-oxide), indolyl, isoquinolyl (or its N-oxide) or quinolyl (or its N-oxide).

A specific value for R_1 is H.

A specific value for R_2 is H.

A specific value for R_3 is H.

A specific value for R_4 is H or OH.

A specific value for R_5 is H.

A specific value for R_6 is OH.

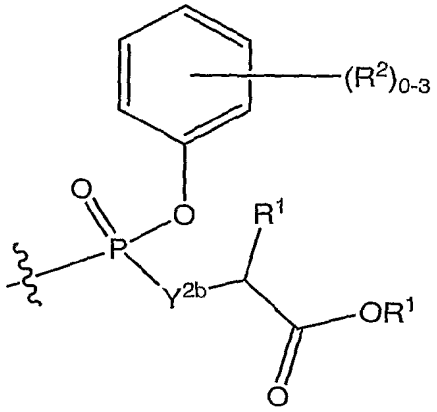
A specific value for each of R_7 and R_8 is H.

A specific value for R_{10} is OH.

A specific value for R_{10} is $-OP(=O)(OH)_2$.

A specific value for R_{10} is a phosphonate.

A specific value for R_{10} has the formula:



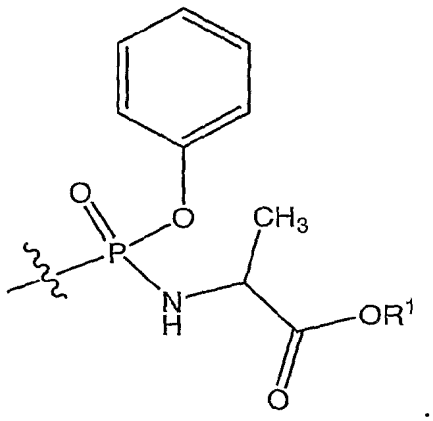
wherein:

Y^{2b} is O or NH;

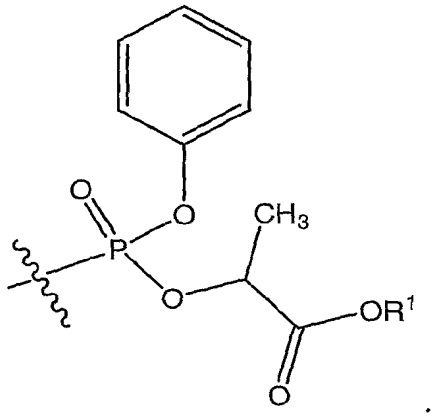
each R^1 is independently H, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkenyl, $(C_1\text{-}C_6)$alkynyl, aryl, $(C_1\text{-}C_6)$alkanoyl, or aryl$(C_1\text{-}C_6)$alkyl; and

each R^2, is independently $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkylthio, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkanoyl, $(C_1\text{-}C_6)$alkanoyloxy, $(C_1\text{-}C_6)$alkoxycarbonyl, cyano, halo, hydroxy, nitro, carboxy, $(C_3\text{-}C_8)$cycloalkyl, $(C_3\text{-}C_8)$cycloalkoxy, trifluoromethoxy, mercapto, or trifluoromethyl.

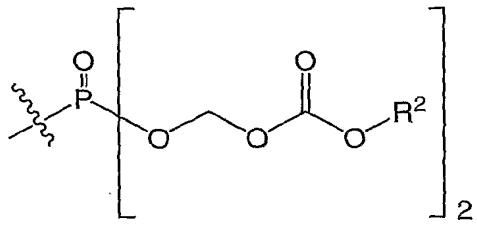
A specific value for R_{10} has the formula:



A specific value for R_{10} has the formula:

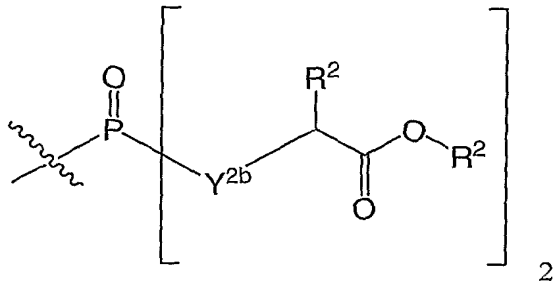


A specific value for R_{10} has the formula:



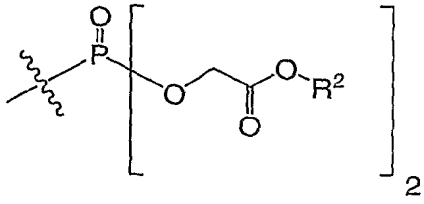
wherein R^2 is $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, or $(C_2\text{-}C_6)$alkynyl.

A specific value for R_{10} has the formula:



wherein: Y^{2b} is O or $N(R^4)$; R^2 is $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, aryl$(C_1\text{-}C_6)$alkyl, or $(C_2\text{-}C_6)$alkynyl; and R^4 is $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, aryl$(C_1\text{-}C_6)$alkyl, or $(C_2\text{-}C_6)$alkynyl.

A specific value for R_{10} has the formula:



In one specific embodiment of the invention, the compound of formula I is not (1'*S*,2'*R*,3'*S*,4'*R*,5'*S*)-4-(6-amino-purin-9-yl)-1-[hydroxymethyl]bi-cyclo[3.1.0]hexane-2,3-diol.

In another specific embodiment of the invention, the compound of formula I is not 4-(6-amino-purin-9-yl)-1-[hydroxymethyl]bi-cyclo[3.1.0]hexane-2,3-diol.

In another specific embodiment of the invention, the compound of formula I is not: (1'*S*,2'*R*,3'*S*,4'*R*,5'*S*)-4-(6-amino-9H-purin-9-yl)-1-[phosphoryloxymethyl]bi-cyclo[3.1.0]hexane-2,3-diol; 5-(6-amino-9H-purin-9-yl)-1-[phosphoryloxymethyl]bicyclo[3.1.0]hexane-2,3-diol; 5-(6-amino-9H-purin-9-yl)-1-[hydoxymethyl]bicyclo[3.1.0]hexane-2,3-diol; (1'*S*,2'*R*,3'*S*,4'*R*,5'*S*)-4-(6-amino-9H-purin-9-yl)-1-[triphosphoryloxymethyl]bi-cyclo[3.1.0]hexane-2,3-diol; 5-(6-amino-9H-purin-9-yl)-1-[triphosphoryloxymethyl]bicyclo[3.1.0]hexane-2,3-diol; (1'*S*,2'*R*,3'*S*,4'*R*,5'*S*)-4-(2,4(*H*,3*H*)-dioxopyrimidin-1-yl)-1-(phosphoryloxymethyl)bi-cyclo[3.1.0]hexane-2,3-diol; (1'*S*,2'*R*,3'*S*,4'*R*,5'*S*)-4-(2,4(*H*,3*H*)-dioxopyrimidin-1-yl)-1- (diphosphoryloxymethyl)bicyclo[3.1.0]hexane-2,3-diol; or

(1'*S*,2'*R*,3'*S*,4'*R*,5'*S*)-4-(2,4(H,3H)-dioxopyrimidin-1-yl)-1-(triphosphoryloxymethyl)bicyclo[3.1.0]hexane-2,3-diol.

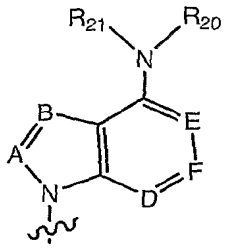
In another specific embodiment of the invention the compounds of formula I exclude compounds *wherein:* R_1 is H; R_2 is H; R_3 is H; R_4 is OH; R_5 is H; R_6 is OH; R_7 and R_8 are each H; R_9 is 6-amino-9H-purin-9-yl or 2,4(*H*,3*H*)-dioxopyrimidin-1-yl; and R_{10} is OH, -OP(=O)(OH)$_2$, -OP(=O)(OH)-P(=O)(OH)$_2$, or -OP(=O)(OH)-P(=O)(OH)-P(=O)(OH)$_2$.

In another sprcific embodiment of the invention the compounds of formula II exclude compounds *wherein:* R_1 is H; R_2 is H; R_3 is H; R_4 is OH; R_5 is H; R_6 is OH; R_7 and R_8 are each H; R_9 is 6-amino-9H-purin-9-yl; and R_{10} is OH, -OP(=O)(OH)$_2$, -OP(=O)(OH)-P(=O)(OH)$_2$, or -OP(=O)(OH)-P(=O)(OH)-P(=O)(OH)$_2$,

Nucleoside base

The invention provides compounds of formula I and II wherein R_9 is a nucleoside base. A multitude of nucleoside base analogs have been reported. The compounds of formula I and II may include any nucleoside base, provided the final compound possesses useful therapeutic (e.g. anti-viral) properties. For example, a specific value for R_9 is a heterocycle or a substituted heterocycle (e.g. a purine, substituted purine, pyrimidine, or a substituted pyrimidine).

Specific nucleoside base structures that can be incorporated into the compounds of the invention include the nucleoside bases reported in United States Patent Application Publication Number 2004/0147464. Accordingly, a specific value for R_9 has the following formula:



wherein:

R_{20} is OH or (C_1-C_6)alkoxy that is optionally substituted with one or more R_{22}; and R_{21} is H or (C_1-C_6)alkyl that is optionally substituted with one or more R_{22}; or R_{20} and R_{21} together with the nitrogen to which they are attached form a heterocyclic ring that is optionally subsitituted with one or more R_{22};

each R_{22} is independently (C_1-C_6)alkyl, (C_1-C_6)alkylthio, (C_1-C_6)alkoxy, (C_1-C_6)alkanoyl, (C_1-C_6)alkanoyloxy, (C_1-C_6)alkoxycarbonyl, $NR_{23}R_{24}$, -C(=O)$NR_{23}R_{24}$, aryl, heteroaryl, cyano, halo, hydroxy, nitro, carboxy, or (C_3-C_8)cycloalkyl;

R_{23} and R_{24} are each independently H, (C_1-C_6)alkyl or (C_1-C_6)alkanoyl;

wherein each aryl or heteroaryl of R_{22} is optionally substituted with one or more (C_1-C_6)alkyl, (C_1-C_6)alkylthio, (C_1-C_6)alkoxy, (C_1-C_6)alkanoyl, (C_1-C_6)alkanoyloxy, (C_1-C_6)alkoxycarbonyl, $NR_{23}R_{24}$, -C(=O)$NR_{23}R_{24}$, cyano, halo, hydroxy, nitro, carboxy, (C_3-C_8)cycloalkyl, trifluoromethoxy, mercapto, or trifluoromethyl; and

A, B, D, F, and E are each independently >N or >C-R_{25};

each R_{25} is independently H, cyano, nitro, (C_1-C_6)alkyl, (C_1-C_6)alkenyl, (C_1-C_6)alkynyl, -$NHCONH_2$, C(=O)$NR_{26}R_{27}$, $COOR_{28}$, hydroxy, (C_1-C_6)alkoxy, -$NR_{26}R_{27}$, halo, 1,3-oxazol-2-yl, 1,3-oxazol-5-yl, 1,3-thiazol-2-yl, imidazol-2-yl, 2-oxo-[1,3]dithiol-4-yl, furan-2-yl, or 2H-[1,2,3]triazol-4-yl;

each R_{26} and R_{27} is independently H, (C_1-C_6)alkyl, (C_1-C_6)alkenyl, (C_1-C_6)alkynyl, (C_3-C_8)cycloalkyl, aryl, heterocycle, hydroxy, (C_1-C_6)alkoxy; or R_{26} and R_{27} together with the nitrogen to which they are attached form a heterocycle; and

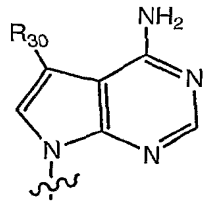
each R_{28} is independently H, (C_1-C_6)alkyl, (C_1-C_6)alkenyl, (C_1-C_6)alkynyl, (C_3-C_8)cycloalkyl, aryl, or heterocycle;

wherein each (C_1-C_6)alkyl, (C_1-C_6)alkenyl, (C_1-C_6)alkynyl, (C_3-C_8)cycloalkyl, aryl, heterocycle, and (C_1-C_6)alkoxy of R_{26} and R_{27} is optionally substituted with one or more (C_1-C_6)alkyl, (C_1-C_6)alkylthio, (C_1-C_6)alkoxy, (C_1-C_6)alkanoyl, (C_1-C_6)alkanoyloxy, (C_1-C_6)alkoxycarbonyl, NH_2, cyano, halo, hydroxy, nitro, carboxy, (C_3-C_8)cycloalkyl, (C_3-C_8)cycloalkoxy, trifluoromethoxy, or mercapto.

A specific value for R_{20} is OH, methoxy, or propoxy; and for R_{21} is H.

A specific value for R_{20} and R_{21} together with the nitrogen to which they are attached form a pyrrolidin-1-yl, 1,3,4,9-tetrahydro-beta-carbolin-2-yl, piperidinyl, azetidinyl, 3,6-dihydro-2H-pyridin-1-yl, or 3,4-dihydro-1H-isoquinolin-2-yl ring, which ring is optionally substituted with $-C(=O)NH_2$.

Specific nucleoside base structures that can be incorporated into the compounds of the invention include the nucleoside bases reported in United States Patent Application Publication Number 2005/0215511. Accordingly, a specific value for R_9 has the following formula:



wherein:

R_{30} is $-C\equiv CR_{31}$, $-CH=CHR_{32}$, formyl, $-CH=NHNR_{33}$, $-CH=N(OR_{33})$, $-CH(OR_{34})$, or $-B(OR_{33})$;

R_{31} is tri(C_1-C_6)alkylsilyl, (C_1-C_6)alkoxy(C_1-C_6)alkyl, heteroaryl, aryl, Carboxy, or (C_1-C_6)alkoxycarbonyl;

R_{32} is hydrogen or *cis*-(C_1-C_6)alkoxy;

R_{33} is H or (C_1-C_6)alkyl; and

R_{34} is (C_1-C_6)alkyl;

wherein each aryl or heteroaryl of R_{31} is optionally substituted with one or more (C_1-C_6)alkyl, (C_1-C_6)alkylthio, (C_1-C_6)alkoxy, (C_1-C_6)alkanoyl, (C_1-C_6)alkanoyloxy, (C_1-C_6)alkoxycarbonyl, $NR_{35}R_{36}$, $-C(=O)NR_{35}R_{36}$, cyano, halo, hydroxy, nitro, carboxy, (C_3-C_8)cycloalkyl, (C_3-C_8)cycloalkoxy, guanidino, trifluoromethoxy, mercapto, $-S(=O)_mR_{37}$, or trifluoromethyl;

m is 0, 1, or 2;

R_{35} and R_{36} are each independently H, (C_1-C_6)alkyl or (C_1-C_6)alkanoyl;

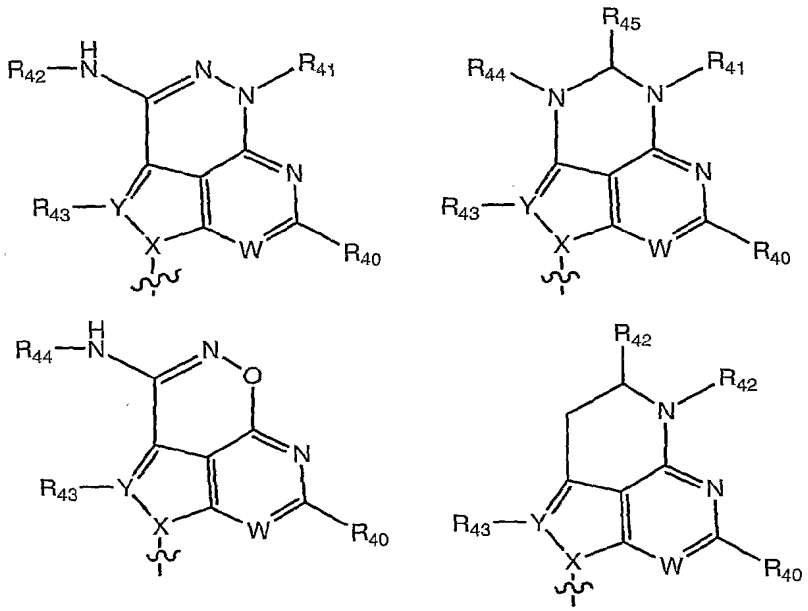
R_{37} is (C_1-C_6)alkyl, aryl, hetrocycle, or $NR_{38}R_{39}$; and

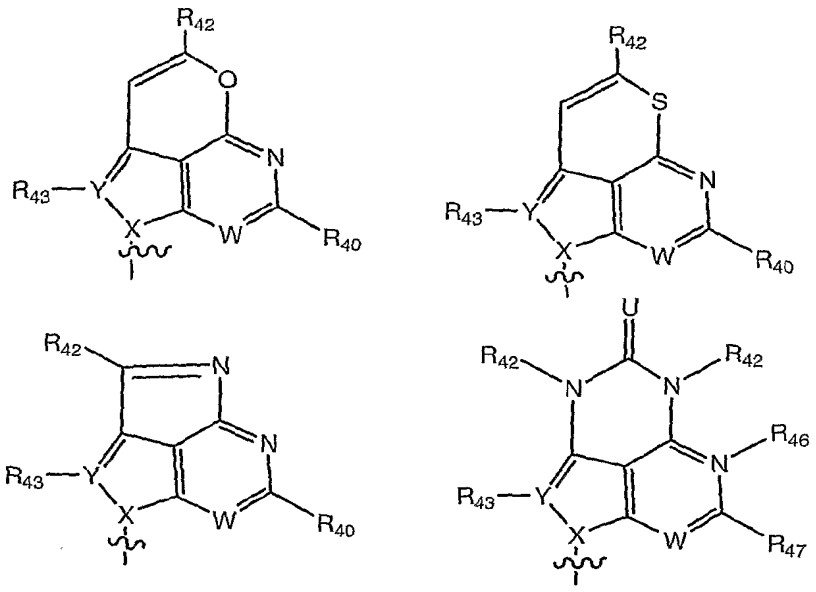
R_{38} and R_{39} are each independently H, (C_1-C_6)alkyl or (C_1-C_6)alkanoyl;

wherein each aryl or heterocycle of R_{37} is optionally substituted with one or more (C_1-C_6)alkyl, (C_1-C_6)alkylthio, (C_1-C_6)alkoxy, (C_1-C_6)alkanoyl, (C_1-C_6)alkanoyloxy, (C_1-C_6)alkoxycarbonyl, $NR_{35}R_{36}$, $-C(=O)NR_{35}R_{36}$, cyano, halo, hydroxy, nitro, carboxy, (C_3-C_8)cycloalkyl, (C_3-C_8)cycloalkoxy, guanidino, trifluoromethoxy, mercapto, or trifluoromethyl.

A specific value for R_{30} is 2-trimethylsilylethynyl, 2-(2-pyridyl)ethynyl, 2-(4-pyridyl)ethynyl, 2-(4-methoxy)ethynyl, 2-(aminocarbonyl)ethynyl, 3,3-diethoxypropyn-1-yl, 2-(dimethylaminocarbonyl)ethynyl, 2-(N-amino(aminocarbonyl)ethynyl, 2-carboxyethynyl, 2-ethoxycarbonylethynyl, 2-methoxycarbonylethynyl, 2-phenylethynyl, 2-(4-fluorophenyl)ethynyl, 2-(4-methylphenyl)ethynyl, vinyl, 2-methoxyvinyl, formyl, $-CH=N-NH_2$, -CH=NOH, 1,1-diisopropoxymethyl, or $-B(OH)_2$.

Specific nucleoside base structures that can be incorporated into the compounds of the invention include the nucleoside bases reported in International Patent Application Publication Number WO 03/061385. Accordingly, a specific value for R_9 has one of the the following formulae:





wherein:

R_{40} is H, $NR_{4a}R_{4b}$, $NHC(=O)R_{4b}$, $(C_1\text{-}C_6)$alkyl$NR_{4a}R_{4b}$, $NHNH_2$, cyano, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, aryl$(C_1\text{-}C_6)$alkyl, heterocycle$(C_1\text{-}C_6)$alkyl, halo, $(C_1\text{-}C_6)$alkylthio, $(C_1\text{-}C_6)$alkoxy, hydroxy, or mercapto;

R_{41} is H, $(C_1\text{-}C_6)$alkyl, hydroxy$(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, heterocycle, aryl, aryl$(C_1\text{-}C_6)$alkyl;

each R_{42} is independently H, hydroxy, mercapto, cyano, $-SNR_{4c}R_{4d}$, $-C(NH)NR_{4c}R_{4d}$, $-C(=NH)NHOH$, $-C(NH)NHO_{4c}$, $-C(=NH)NHNR_{4c}R_{4d}$, $NHCOR_{4c}$, SR_{4c}, OR_{4c}, SOR_{4c}, SO_2R_{4c}, $-C(=O)NR_{4c}R_{4d}$, $-C(=S)NR_{4c}R_{4d}$, or R_{4c};

R_{43} is H, hydroxy, $NR_{4c}R_{4d}$, $NHC(=O)NR_{4c}$, $NHNHR_{4c}$, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, heterocycle, aryl, aryl$(C_1\text{-}C_6)$alkyl, halo, $COOR_{4c}$, $CONR_{4c}R_{4d}$, or absent when Y is N;

R_{4a} and R_{4b} are each independently hydrogen, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, heterocycle, or aryl;

R_{4c}, and R_{4d} are each independently hydrogen, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, heterocycle, or aryl;

X, Y, and W are each independently N, C, CR_{4c}, S or P;

R_{44} is H, hydroxy, mercapto, cyano, -$SNR_{4c}R_{4d}$, -$C(NH)NR_{4c}R_{4d}$, -$C(=NH)NHOH$, -$C(NH)NHOR_{4c}$, -$C(=NH)NHNR_{4c}R_{4d}$, $NHCOR_{4c}$, SR_{4c}, OR_{4c}, SOR_{4c}, SO_2R_{4c}, -$C(=O)NR_{4c}R_{4d}$, -$C(=S)NR_{4c}R_{4d}$, or R_{4c};

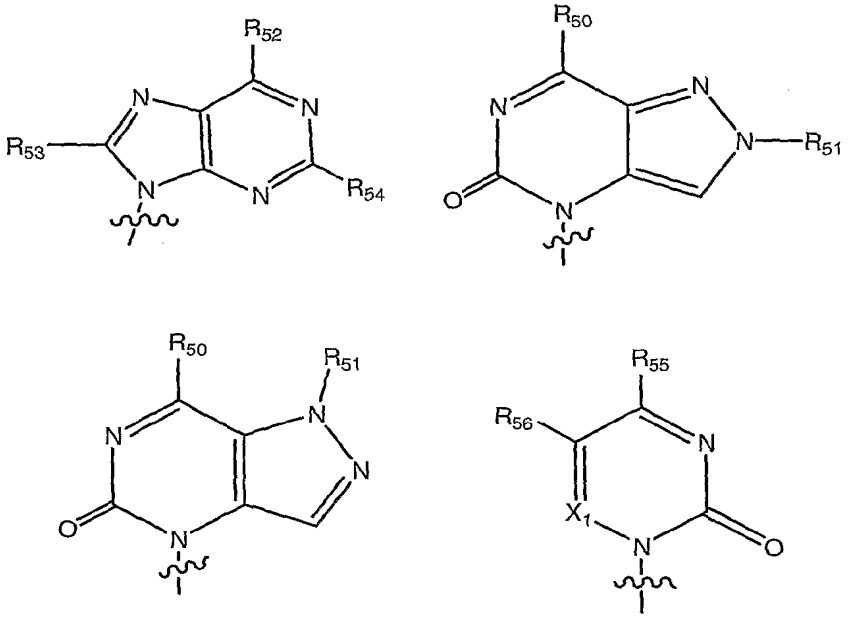
R_{45} is H, hydroxy, mercapto, cyano, -$SNR_{4c}R_{4d}$, -$C(NH)NR_{4c}R_{4d}$, -$C(=NH)NHOH$, -$C(NH)NHO_{4c}$, -$C(=NH)NHNR_{4c}R_{4d}$, $NHCOR_{4c}$, SR_{4c}, OR_{4c}, SOR_{4c}, SO_2R_{4c}, -$C(=O)NR_{4c}R_{4d}$, -$C(=S)NR_{4c}R_{4d}$, or R_{4c};

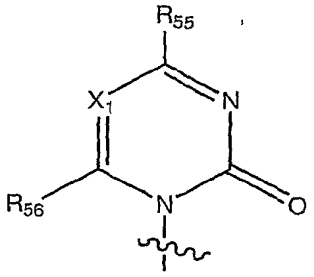
R_{46}, and R_{47} together with the atoms to which they are attached form a heterocyclic ring; and

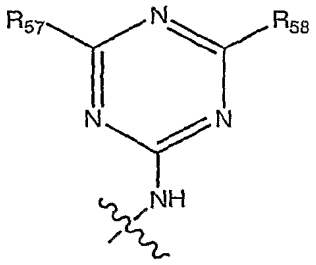
U is S or O;

wherein each aryl or heterocycle is optionally substituted with one or more (C_1-C_6)alkyl, (C_1-C_6)alkylthio, (C_1-C_6)alkoxy, (C_1-C_6)alkanoyl, (C_1-C_6)alkanoyloxy, (C_1-C_6)alkoxycarbonyl, cyano, halo, hydroxy, nitro, carboxy, (C_3-C_8)cycloalkyl, (C_3-C_8)cycloalkoxy, trifluoromethoxy, mercapto, or trifluoromethyl.

Specific nucleoside base structures that can be incorporated into the compounds of the invention include the nucleoside bases reported in International Patent Application Publication Number WO 03/062257. Accordingly, a specific value for R_9 has one of the following formulae:







wherein:

R_{50} is $NR_{5a}R_{5b}$, $ONR_{5a}R_{5b}$, $NR_{5a}NR_{5a}R_{5b}$, SR_{5b}, OR_{5b}, H, hydroxy, (C_1-C_6)alkyl, (C_1-C_6)alkenyl, (C_1-C_6)alkynyl, or aryl;

R_{51} is (C_1-C_6)alkyl, (C_1-C_6)alkanoyl, or aryl;

R_{52} is (C_1-C_6)alkyl, (C_1-C_6)alkenyl, (C_1-C_6)alkynyl, or aryl;

R_{53} is H, halo, (C_1-C_6)alkyl, (C_1-C_6)alkenyl, (C_1-C_6)alkynyl, or aryl;

R_{54} is H or NH_2;

R_{55} is $NR_{5a}R_{5b}$, $ONR_{5a}R_{5b}$, $NR_{5a}NR_{5a}R_{5b}$, SR_{5b}, OR_{5b}, H, hydroxy, (C_1-C_6)alkyl, (C_1-C_6)alkenyl, (C_1-C_6)alkynyl, or aryl;

R_{56} is H, halo, (C_1-C_6)alkyl, or (C_1-C_6)alkenyl;

R_{57} and R_{58} are each independently –L-R_{5c};

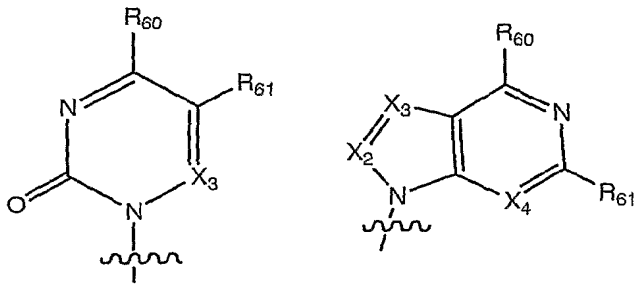
each L is independently a direct bond, -N(R_{5a})-, O or S;

each R_{5a} and R_{5b} is independently H, hydroxy, (C_1-C_6)alkyl, (C_1-C_6)alkenyl, (C_1-C_6)alkynyl, or aryl; and

each R_{5c} is $NR_{5a}R_{5b}$, H, hydroxy, (C_1-C_6)alkyl, (C_1-C_6)alkenyl, (C_1-C_6)alkynyl, or aryl;

wherein each (C_1-C_6)alkyl, (C_1-C_6)alkenyl, (C_1-C_6)alkynyl, or aryl of R_{50}-R_{58} and R_{5a}-R_{5c} is optionally substituted with one or more (C_1-C_6)alkyl, (C_1-C_6)alkylthio, (C_1-C_6)alkoxy, (C_1-C_6)alkanoyl, (C_1-C_6)alkanoyloxy, (C_1-C_6)alkoxycarbonyl, cyano, halo, hydroxy, nitro, carboxy, (C_3-C_8)cycloalkyl, (C_3-C_8)cycloalkoxy, trifluoromethoxy, mercapto, or trifluoromethyl.

Specific nucleoside base structures that can be incorporated into the compounds of the invention include the nucleoside bases reported in International Patent Application Publication Number WO 03/072757. Accordingly, a specific value for R_9 has one of the following formulae:



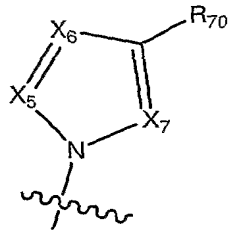
wherein:

X_2, X_3, and X_4, are each independently N, CH, or C-R_{6a};

R_{60}, R_{61}, and R_{6a} are each independently H, halo, $NR_{6b}R_{6c}$, hydroxyamino, $NR_{6b}NR_{6b}R_{6c}$, N_3, NO, NO_2, formyl, cyano, -C(=O)$NR_{6b}R_{6c}$, -C(=S)$NR_{6b}R_{6c}$, -C(=O)OR_{6b}, R_{6b}, OR_{6b}, or SR_{6b}; and

R_{6b}, and R_{6c} are each independently H, (C_1-C_6)alkyl, (C_1-C_6)alkenyl, (C_1-C_6)alkynyl, aryl, (C_1-C_6)alkanoyl, or aryl(C_1-C_6)alkyl.

Specific nucleoside base structures that can be incorporated into the compounds of the invention include the nucleoside bases reported in International Patent Application Publication Number WO 03/073989. Accordingly, a specific value for R_9 has the following formula:



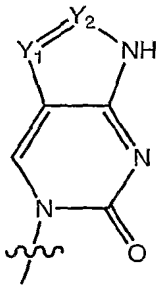
wherein:

X_5, X_6, and X_7, are each independently N, CH, or C-R_{7a};

R_{70} and R_{7a} are each independently H, halo, $NR_{7b}R_{7c}$, hydroxyamino, $NR_{7b}NR_{7b}R_{7c}$, N_3, NO, NO_2, formyl, cyano, -C(=O)$NR_{7b}R_{7c}$, -C(=S)$NR_{7b}R_{7c}$, -C(=O)OR_{7b}, R_{7b}, OR_{7b}, or SR_{7b}; and

R_{7b}, and R_{7c} are each independently H, (C_1-C_6)alkyl, (C_1-C_6)alkenyl, (C_1-C_6)alkynyl, aryl, (C_1-C_6)alkanoyl, or aryl(C_1-C_6)alkyl.

Specific nucleoside base structures that can be incorporated into the compounds of the invention include the nucleoside bases reported in International Patent Application Publication Number WO 2004/080466. Accordingly, a specific value for R_9 has the following formula:

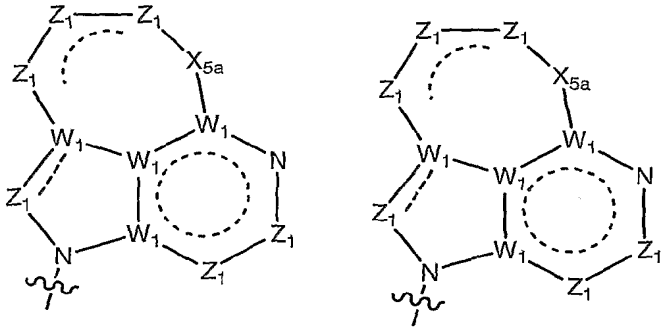


wherein:

Y_1=Y_2 is –N=N-, -CH=N-, -N=CR_{8a}-, or –CH=CR_{8a}-; and

each R_{8a} is independently H, halo, or (C_1-C_6)alkyl.

Specific nucleoside base structures that can be incorporated into the compounds of the invention include the nucleoside bases reported in International Patent Application Publication Number WO 2005/021568. Accordingly, a specific value for R_9 has one of the following formulae:



wherein:

each Z_1 is independently N, C-R_{9a}, O, S, NR_{9b}, >C=O, >C=S, >C=NR_{9b}, >S=O, >S(O)$_2$ or CH-R_{9a}; provided that if a Z_1 participates in an optional bond represented by a dotted line --- in the formula, then that Z_1 is N or C-R_{9a}; and provided that if a Z_1 does not participate in an optional bond represented by a

dotted line --- in the formula, then that Z_1 is O, S, NR_{9b}, >C=O, >C=S, >C=NR_{9b}, >S=O, >$S(O)_2$ or CH-R_{9a};

X_{5a} is O, S, SO, SO_2, Se, SeO, SeO_2 or NR_{9b};

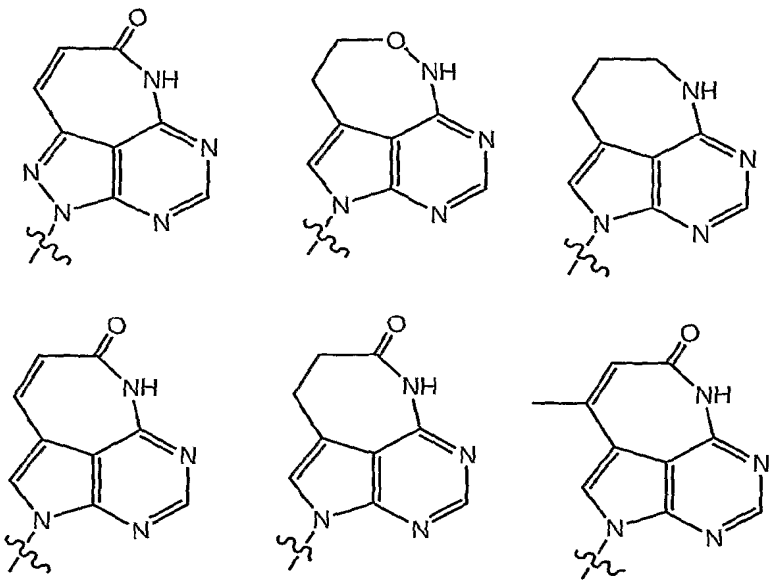
each W_1 is C, CH, or N; wherein if a W_1 participates in an optional bond represented by a dotted line --- in the formula, then that W_1 is C; and if a W_1 does not participate in an optional bond represented by a dotted line --- in the formula, then that W_1 is CH, or N;

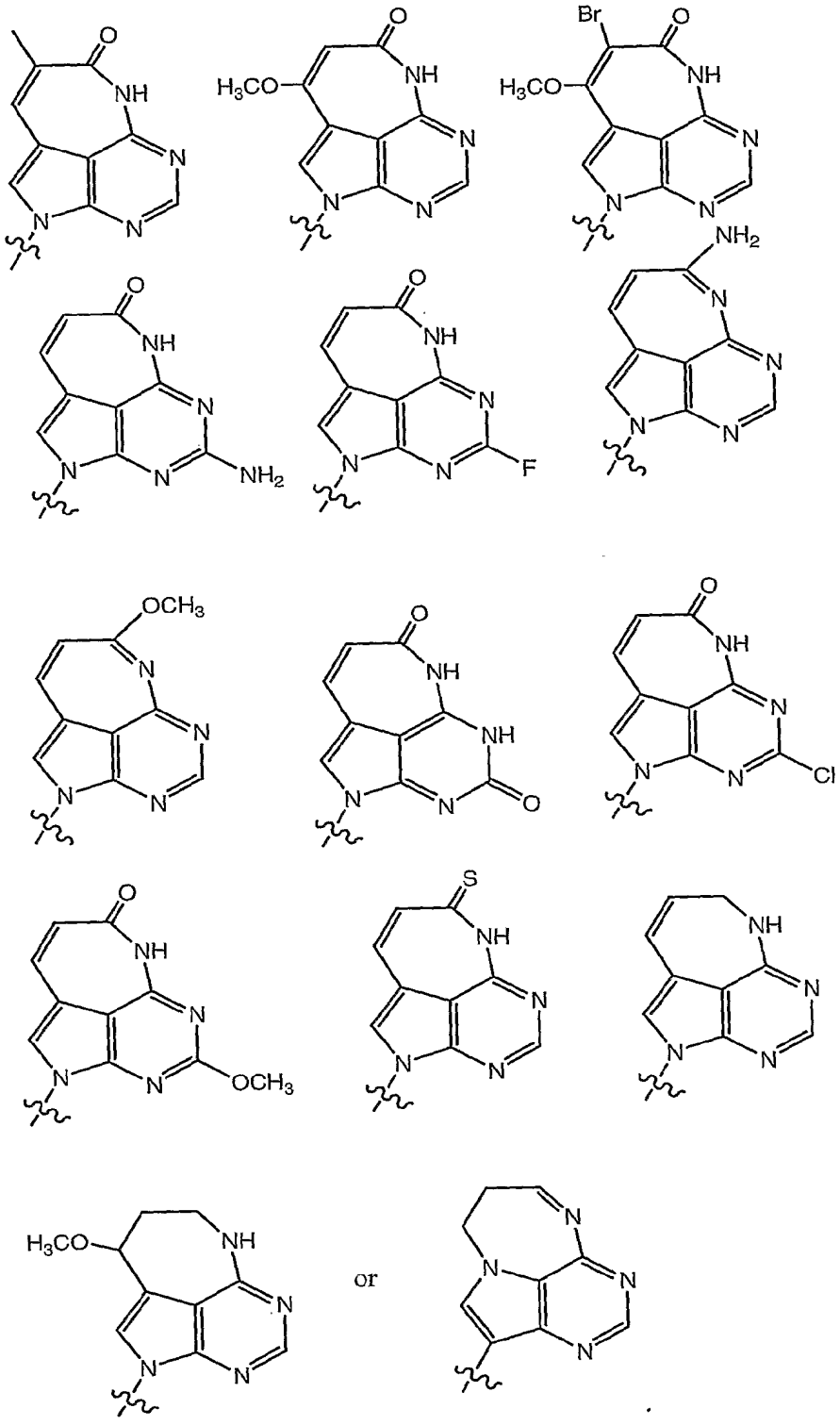
each R_{9a} is independently H, halo, $NR_{9c}R_{9d}$, hydroxyamino, $NR_{9c}NR_{9c}R_{9d}$, N_3, cyano, -C(=O)$NR_{9c}R_{9d}$, -C(=S)$NR_{9c}R_{9d}$, -C(=S)$NR_{9c}R_{9d}$, -C(=NH)OR_{9c}, R_{9c}, OR_{9c}, or SR_{9c};

each R_{9b} is independently H, (C_1-C_6)alkyl, (C_1-C_6)alkenyl, (C_1-C_6)alkynyl, aryl, (C_1-C_6)alkanoyl, or aryl(C_1-C_6)alkyl; and

R_{9c}, and R_{9d} are each independently H, (C_1-C_6)alkyl, (C_1-C_6)alkenyl, (C_1-C_6)alkynyl, aryl, (C_1-C_6)alkanoyl, or aryl(C_1-C_6)alkyl.

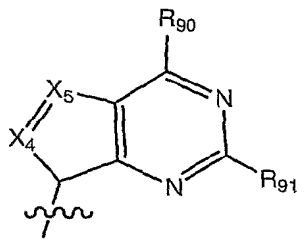
Another specific value for R_9 has one of the following formulae:





or

Specific nucleoside base structures that can be incorporated into the compounds of the invention include the nucleoside bases reported in International Patent Application Publication Number WO 2005/123087. Accordingly, a specific value for R_9 has one of the following formulae:



wherein:

X_4 is CR_{90a} or N;

X_5 is O, S, or NR_{91a};

R_{90} and R_{91} are each independently H, halo, hydroxy, $(C_1\text{-}C_6)$alkoxy, $NR_{90b}R_{91b}$, or heterocycle;

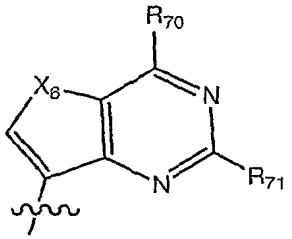
R_{90a} is H, halo, methyl, azido, or amino;

R_{91a} is H, or $(C_1\text{-}C_6)$alkyl; and

R_{90b} and R_{91b} are each independently H, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_8)$cycloalkyl, or aryl$(C_1\text{-}C_6)$alkyl;

wherein each $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_8)$cycloalkyl, aryl$(C_1\text{-}C_6)$alkyl, and heterocycle of R_{90}-R_{91}, R_{91a}, and R_{90b}-R_{91b} are optionally substituted with one or more (e.g. 1, 2, 3, or 4) halo, hydroxy, amino, $(C_1\text{-}C_6)$alkyl, and $(C_1\text{-}C_6)$alkoxy.

Specific nucleoside base structures that can be incorporated into the compounds of the invention include the nucleoside bases reported in International Patent Application Publication Number WO 2006/002231. Accordingly, a specific value for R_9 is a 9-deazapurine derivative, such as, for example, a group of the following formulae:



wherein:

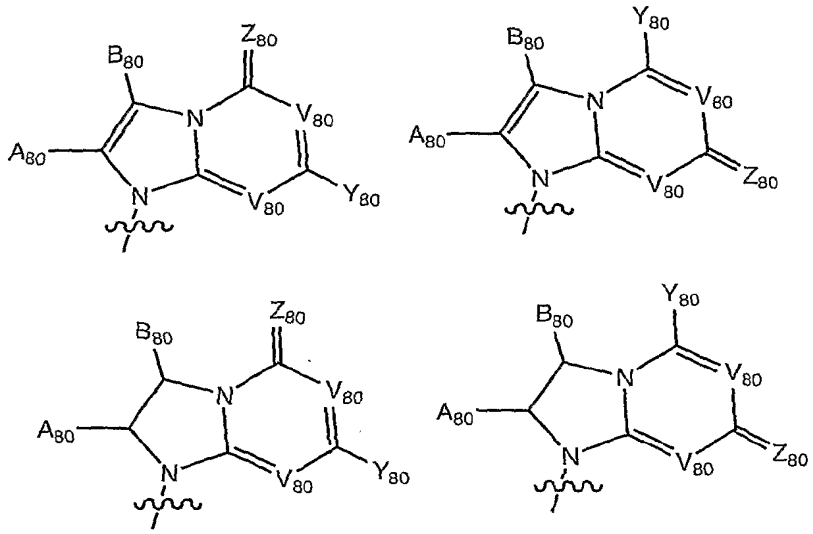
X_6 is O, S, or NR_{70a};

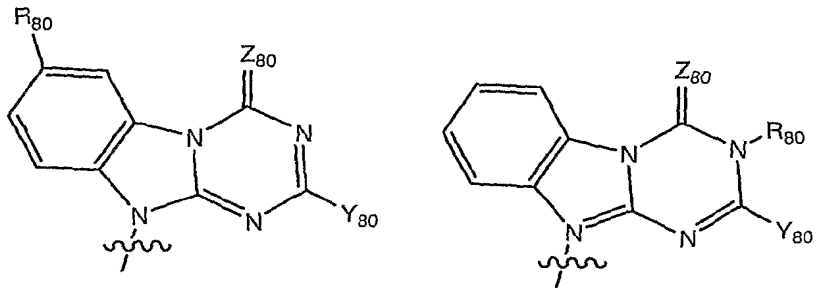
R_{70} and R_{71} are each independently H, halo, hydroxy, mercapto, aryl, heterocycle, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkenyl, $(C_1\text{-}C_6)$alkynyl, $(C_1\text{-}C_6)$alkylthio, arylthio, $-S(=O)(C_1\text{-}C_6)$alkyl, $-S(=O)_2(C_1\text{-}C_6)$alkyl, $-S(=O)_2NR_{70b}R_{71b}$, $NR_{70b}R_{71b}$, $(C_1\text{-}C_6)$alkoxy, aryloxy, (heterocycle)oxy;

R_{70a} is H, methyl, ethyl, or acetyl; and

R_{70b} and R_{71b} are each independently H, $(C_1\text{-}C_6)$alkyl, aryl, aryl$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkanoyl, or aryl-C(=O)-;

Specific nucleoside base structures that can be incorporated into the compounds of the invention include the nucleoside bases reported in International Patent Application Publication Number WO 2006/000922. Accordingly, a specific value for R_9 a specific value for R_9 has one of the following formulae:





wherein:

A_{80}, B_{80}, and Y_{80}, are each independently H, halo, OR_{80}, $S(O)_nR_{80}$, $NR_{80}R_{81}$, cyano, trifluoromethyl, $C(=W)OR_{80}$, $C(=W)SR_{80}$, $C(=W)NR_{80}$ R_{81}, nitro, azido, carbocyclic, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkenyl, $(C_1\text{-}C_6)$alkynyl, aryl, aryl$(C_1\text{-}C_6)$alkyl, or heterocycle; or A_{80} and B_{80} taken together with the carbon atoms to which they are attached from a 4-7 membered carbocyclic or heterocyclic ring;

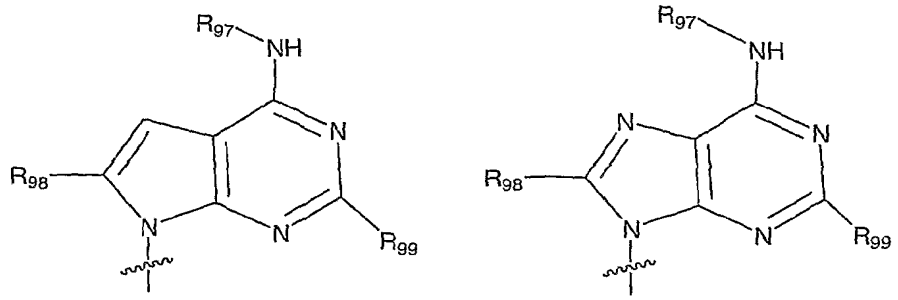
n is 0, 1, or 2

Z_{80} is O, S, NR_{80}, or $CR_{80}R_{81}$;

each V is independently N or CR_{80}; and

each R_{80} and R_{81} is independently H, carbocycle, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkenyl, $(C_1\text{-}C_6)$alkynyl, halo, $(C_1\text{-}C_6)$alkoxy, amino, methylamino, dimethylamino, cyano, $(C_1\text{-}C_6)$alkanoyl, aryl, aryl$(C_1\text{-}C_6)$alkyl, an amino acid residue (e.g. a natural amino acid residue) or heterocycle; or R_{80} and R_{81} taken together with the atom(s) to which they are attached form a 3-7 membered carbocyclic or heterocyclic ring.

Another specific value for R_9 has one of the following formulae:



wherein:

R_{97} is H, hydroxy, mercapto, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, $(C_2\text{-}C_6)$alkenyl, $(C_3\text{-}C_8)$cycloalkyl, aryl$(C_1\text{-}C_6)$alkyl, aryl or $(C_2\text{-}C_6)$alkynyl;

R_{98} is H, hydroxy, mercapto, or $(C_1\text{-}C_6)$alkyl;

R_{99} is H, halo, azido, cyano, nitro, OR_{99a}, SR_{99a}, $NR_{99b}R_{99c}$, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_3\text{-}C_8)$cycloalkyl, aryl$(C_1\text{-}C_6)$alkyl, aryl or $(C_2\text{-}C_6)$alkynyl;

each R_{99a} is independently H, $(C_1\text{-}C_6)$alkyl, or $(C_1\text{-}C_6)$alkanoyl;

each R_{99b} and R_{99c} is independently H, $(C_1\text{-}C_6)$alkyl, or $(C_1\text{-}C_6)$alkanoyl;

wherein each $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy $(C_1\text{-}C_6)$alkenyl, $(C_1\text{-}C_6)$alkynyl, $(C_3\text{-}C_8)$cycloalkyl, aryl, and aryl$(C_1\text{-}C_6)$alkyl of R_{97}, R_{98}, R_{99}, R_{99a}, R_{99b}, and R_{99c}, is optionally substituted with one or more $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkylthio, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkanoyl, $(C_1\text{-}C_6)$alkanoyloxy, $(C_1\text{-}C_6)$alkoxycarbonyl, NH_2, cyano, azido, halo, hydroxy, nitro, carboxy, trifluoromethoxy, aryl, or mercapto.

Another specific value for R_9 is adenine, guanine, cytosine, uracil, thymine, 7-deazaadenine, 7-deazaguanine, 7-deaza-8-azaguanine, 7-deaza-8-azaadenine, inosine, nebularine, nitropyrrole, nitroindole, 2-aminopurine, 2-amino-6-chloropurine, 2,6-diaminopurine, hypoxanthine, pseudouridine, pseudocytosine, pseudoisocytosine, 5-propynylcytosine, isocytosine, isoguanine, 7-deazaguanine, 2-thiopyrimidine, 6-thioguanine, 4-thiothymine, 4-thiouracil, O^6-methylguanine, N^6-methyladenine, O^4-methylthymine, 5,6-dihydrothymine, 5,6-dihydrouracil, 4-methylindole, substituted triazole, or pyrazolo[3,4-D]pyrimidine;

Another specific value for R_9 is 6-amino-2-chloro-purin-9-yl; 6-amino-2-iodo-purin-9-yl; 6-amino-2-fluoro-purin-9-yl; 6-amino-2-methylthio-purin-9-yl; 6-amino-purin-9-yl; or 4-amino-7H-pyrrolo[2,3-d]pyrimidin-7-yl.

Another specific value for R_9 is adenine or cytosine, which adenine or cytosine is optionally substituted with one or more (C_1-C_6)alkyl, (C_1-C_6)alkylthio, (C_1-C_6)alkoxy, (C_1-C_6)alkanoyl, (C_1-C_6)alkanoyloxy, (C_1-C_6)alkoxycarbonyl, NH_2, cyano, halo, hydroxy, nitro, carboxy, trifluoromethoxy, aryl, or mercapto.

Stereoisomers

The compounds of the invention may have chiral centers, *e.g.*, chiral carbon or phosphorus atoms. The compounds of the invention thus include racemic mixtures of all stereoisomers, including enantiomers, diastereomers, and atropisomers. In addition, the compounds of the invention include enriched or resolved optical isomers at any or all asymmetric, chiral atoms. In other words, the chiral centers apparent from the depictions are provided as the chiral isomers or racemic mixtures. Both racemic and diastereomeric mixtures, as well as the individual optical isomers isolated or synthesized, substantially free of their enantiomeric or diastereomeric partners, are all within the scope of the invention. Stereochemical definitions and conventions used herein generally follow S. P. Parker, Ed., McGraw-Hill Dictionary of Chemical Terms (1984) McGraw-Hill Book Company, New York; and Eliel, E. and Wilen, S., Stereochemistry of Organic Compounds (1994) John Wiley & Sons, Inc., New York.

A single stereoisomer, *e.g.*, an enantiomer, substantially free of its stereoisomer may be obtained by resolution of the racemic mixture using a method such as formation of diastereomers using optically active resolving agents (Stereochemistry of Carbon Compounds, (1962) by E. L. Eliel, McGraw Hill; Lochmuller, C. H., (1975) *J. Chromatogr.*, 113:(3) 283-302). Racemic mixtures of chiral compounds of the invention can be separated and isolated by any suitable method, including: (1) formation of ionic, diastereomeric salts with chiral compounds and separation by fractional crystallization or other methods, (2) formation of diastereomeric compounds with chiral derivatizing reagents, separation of the diastereomers, and conversion to the pure stereoisomers, and (3) separation of the substantially pure or enriched stereoisomers directly under chiral conditions.

Under method (1), diastereomeric salts can be formed by reaction of enantiomerically pure chiral bases such as brucine, quinine, ephedrine, strychnine, α-methyl-β-phenylethylamine (amphetamine), and the like with asymmetric compounds bearing acidic functionality, such as carboxylic acid and sulfonic acid. The diastereomeric salts may be induced to separate by fractional crystallization or ionic chromatography. For separation of the optical isomers of amino compounds, addition of chiral carboxylic or sulfonic acids, such as camphorsulfonic acid, tartaric acid, mandelic acid, or lactic acid can result in formation of the diastereomeric salts.

Alternatively, by method (2), the substrate to be resolved is reacted with one enantiomer of a chiral compound to form a diastereomeric pair (Eliel, E. and Wilen, S. (1994) Stereochemistry of Organic Compounds, John Wiley & Sons, Inc., p. 322). Diastereomeric compounds can be formed by reacting asymmetric compounds with enantiomerically pure chiral derivatizing reagents, such as menthyl derivatives, followed by separation of the diastereomers and hydrolysis to yield the free, enantiomerically enriched xanthene. A method of determining optical purity involves making chiral esters, such as a menthyl ester, *e.g.*, (-) menthyl chloroformate in the presence of base, or Mosher ester, α-methoxy-α-(trifluoromethyl)phenyl acetate (Jacob III. (1982) *J. Org. Chem.* 47:4165), of the racemic mixture, and analyzing the NMR spectrum for the presence of the two atropisomeric diastereomers. Stable diastereomers of atropisomeric compounds can be separated and isolated by normal- and reverse-phase chromatography following methods for separation of atropisomeric naphthyl-isoquinolines (Hoye, T., WO 96/15111).

By method (3), a racemic mixture of two enantiomers can be separated by chromatography using a chiral stationary phase (Chiral Liquid Chromatography (1989) W. J. Lough, Ed. Chapman and Hall, New York; Okamoto, (1990) *J. of Chromatogr.* 513:375-378). Enriched or purified enantiomers can be distinguished by methods used to distinguish other chiral molecules with asymmetric carbon atoms, such as optical rotation and circular dichroism.

The compounds of the invention can also exist as tautomeric isomers in certain cases. Although only one delocalized resonance structure may be

depicted, all such forms are contemplated within the scope of the invention. For example, ene-amine tautomers can exist for purine, pyrimidine, imidazole, guanidine, amidine, and tetrazole systems and all their possible tautomeric forms are within the scope of the invention.

Salts and Hydrates

The compositions of this invention optionally comprise salts of the compounds herein, especially pharmaceutically acceptable non-toxic salts containing, for example, Na^+, Li^+, K^+, Ca^{+2} and Mg^{+2}. Such salts may include those derived by combination of appropriate cations such as alkali and alkaline earth metal ions or ammonium and quaternary amino ions with an acid anion moiety, typically a carboxylic acid. Monovalent salts maybe preferred if a water soluble salt is desired.

Metal salts typically are prepared by reacting the metal hydroxide with a compound of this invention. Examples of metal salts which are prepared in this way are salts containing Li^+, Na^+, and K^+. A less soluble metal salt can be precipitated from the solution of a more soluble salt by addition of the suitable metal compound.

In addition, salts may be formed from acid addition of certain organic and inorganic acids, *e.g.*, HCl, HBr, H_2SO_4, H_3PO_4 or organic sulfonic acids, to basic centers, typically amines, or to acidic groups. Finally, it is to be understood that the compositions herein comprise compounds of the invention in their un-ionized, as well as zwitterionic form, and combinations with stoichiometric amounts of water as in hydrates.

Also included within the scope of this invention are the salts of the parental compounds with one or more amino acids. Any amino acid can be used, especially the naturally-occurring amino acids found as protein components, although the amino acid typically is one bearing a side chain with a basic or acidic group, *e.g.*, lysine, arginine or glutamic acid, or a neutral group such as glycine, serine, threonine, alanine, isoleucine, or leucine.

For therapeutic use, salts of active ingredients of the compounds of the invention will typically be physiologically acceptable, *i.e.* they will be salts derived from a physiologically acceptable acid or base. However, salts of acids

or bases which are not physiologically acceptable may also find use, for example, in the preparation or purification of a physiologically acceptable compound. All salts, whether or not derived form a physiologically acceptable acid or base, are within the scope of the present invention.

Pharmaceutical Formulations

Pharmaceutical formulations according to the present invention comprise one or more compounds of the invention together with one or more pharmaceutically acceptable carriers or excipients and optionally other therapeutic agents. Pharmaceutical formulations containing the active ingredient may be in any form suitable for the intended method of administration. When used for oral use for example, tablets, troches, lozenges, aqueous or oil suspensions, dispersible powders or granules, emulsions, hard or soft capsules, syrups or elixirs may be prepared. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents including sweetening agents, flavoring agents, coloring agents and preserving agents, in order to provide a palatable preparation. Tablets containing the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for manufacture of tablets are acceptable. These excipients may be, for example, inert diluents, such as calcium or sodium carbonate, lactose, lactose monohydrate, croscarmellose sodium, povidone, calcium or sodium phosphate; granulating and disintegrating agents, such as maize starch, or alginic acid; binding agents, such as cellulose, microcrystalline cellulose, starch, gelatin or acacia; and lubricating agents, such as magnesium stearate, stearic acid or talc. Tablets may be uncoated or may be coated by known techniques including microencapsulation to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate alone or with a wax may be employed.

Formulations for oral use may be also presented as hard gelatin capsules where the active ingredient is mixed with an inert solid diluent, for example calcium phosphate or kaolin, or as soft gelatin capsules wherein the active

ingredient is mixed with water or an oil medium, such as peanut oil, liquid paraffin or olive oil.

Aqueous suspensions of the invention contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients include a suspending agent, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropyl methylcelluose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia, and dispersing or wetting agents such as a naturally occurring phosphatide (*e.g.*, lecithin), a condensation product of an alkylene oxide with a fatty acid (*e.g.*, polyoxyethylene stearate), a condensation product of ethylene oxide with a long chain aliphatic alcohol (*e.g.*, heptadecaethyleneoxycetanol), a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride (*e.g.*, polyoxyethylene sorbitan monooleate). The aqueous suspension may also contain one or more preservatives such as ethyl or n-propyl p-hydroxy-benzoate, one or more coloring agents, one or more flavoring agents and one or more sweetening agents, such as sucrose or saccharin.

Oil suspensions may be formulated by suspending the active ingredient in a vegetable oil, such as arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oral suspensions may contain a thickening agent, such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an antioxidant such as ascorbic acid.

Dispersible powders and granules of the invention suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent, and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those disclosed above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, a mineral oil, such as liquid paraffin, or a mixture of

these. Suitable emulsifying agents include naturally-occurring gums, such as gum acacia and gum tragacanth, naturally occurring phosphatides, such as soybean lecithin, esters or partial esters derived from fatty acids and hexitol anhydrides, such as sorbitan monooleate, and condensation products of these partial esters with ethylene oxide, such as polyoxyethylene sorbitan monooleate. The emulsion may also contain sweetening and flavoring agents. Syrups and elixirs may be formulated with sweetening agents, such as glycerol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, a flavoring or a coloring agent.

The pharmaceutical compositions of the invention may be in the form of a sterile injectable preparation, such as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, such as a solution in 1,3-butane-diol or prepared as a lyophilized powder. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile fixed oils may conventionally be employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid may likewise be used in the preparation of injectables.

The amount of active ingredient that may be combined with the carrier material to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a time-release formulation intended for oral administration to humans may contain approximately 1 to 1000 mg of active material compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95% of the total compositions (weight:weight). The pharmaceutical composition can be prepared to provide easily measurable amounts for administration. For example, an aqueous solution intended for intravenous infusion may contain from about 3 to 500 μg of the active ingredient per milliliter of solution in order that infusion of a suitable volume at a rate of about 30 mL/hr can occur.

Formulations suitable for administration to the eye include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the active ingredient. The active ingredient is preferably present in such formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10% particularly about 1.5% w/w.

Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavored basis, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Formulations for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate.

Formulations suitable for intrapulmonary or nasal administration have a particle size for example in the range of 0.1 to 500 microns (including particle sizes in a range between 0.1 and 500 microns in increments microns such as 0.5, 1, 30 microns, 35 microns, etc.), which is administered by rapid inhalation through the nasal passage or by inhalation through the mouth so as to reach the alveolar sacs. Suitable formulations include aqueous or oily solutions of the active ingredient. Formulations suitable for aerosol or dry powder administration may be prepared according to conventional methods and may be delivered with other therapeutic agents such as compounds heretofore used in the treatment or prophylaxis of viral infections as described below.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents.

The formulations can be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried

(lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injection, immediately prior to use. Extemporaneous injection solutions and suspensions are prepared from sterile powders, granules and tablets of the kind previously described. Preferred unit dosage formulations are those containing a daily dose or unit daily sub-dose, as herein above recited, or an appropriate fraction thereof, of the active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

The invention further provides veterinary compositions comprising at least one active ingredient as above defined together with a veterinary carrier therefor.

Veterinary carriers are materials useful for the purpose of administering the composition and may be solid, liquid or gaseous materials which are otherwise inert or acceptable in the veterinary art and are compatible with the active ingredient. These veterinary compositions may be administered orally, parenterally or by any other desired route.

Compounds of the invention can also be formulated to provide controlled release of the active ingredient(s) to allow less frequent dosing or to improve the pharmacokinetic or toxicity profile of the active ingredient(s). Accordingly, the invention also provided compositions comprising one or more compounds of the invention formulated for sustained or controlled release.

An effective dose of active ingredient depends at least on the nature of the condition being treated, toxicity, whether the compound is being used prophylactically (lower doses) or against an active viral infection, the method of delivery, and the pharmaceutical formulation, and will be determined by the clinician using conventional dose escalation studies. It can be expected to be from about 0.0001 to about 100 mg/kg body weight per day. Typically, from about 0.01 to about 10 mg/kg body weight per day. More typically, from about .01 to about 5 mg/kg body weight per day. More typically, from about .05 to about 0.5 mg/kg body weight per day. For example, the daily candidate dose for an adult human of approximately 70 kg body weight will range from 1 mg to

1000 mg, preferably between 5 mg and 500 mg, and may take the form of single or multiple doses.

Routes of Administration

One or more compounds of the invention (herein referred to as the active ingredients) are administered by any route appropriate to the condition to be treated. Suitable routes include oral, rectal, nasal, topical (including buccal and sublingual), vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural), and the like. It will be appreciated that the preferred route may vary with for example the condition of the recipient. An advantage of the compounds of this invention is that they are orally bioavailable and can be dosed orally.

Combination Therapy

Active ingredients of the invention can also be used in combination with other active ingredients. Such combinations are selected based on the condition to be treated, cross-reactivities of ingredients and pharmaco-properties of the combination. For example, when treating a viral infection the compositions of the invention can be combined with other agents that are effective to treat a viral infection (such as other antiviral agents).

It is also possible to combine any compound of the invention with one or more other active ingredients in a unitary dosage form for simultaneous or sequential administration to a patient. The combination therapy may be administered as a simultaneous or sequential regimen. When administered sequentially, the combination may be administered in two or more administrations.

The combination therapy may provide "synergy" and "synergistic effect", *i.e.* the effect achieved when the active ingredients used together is greater than the sum of the effects that results from using the compounds separately. A synergistic effect may be attained when the active ingredients are: (1) co-formulated and administered or delivered simultaneously in a combined formulation; (2) delivered by alternation or in parallel as separate formulations; or (3) by some other regimen. When delivered in alternation therapy, a synergistic effect may be attained when the compounds are administered or

delivered sequentially, *e.g.*, in separate tablets, pills or capsules, or by different injections in separate syringes. In general, during alternation therapy, an effective dosage of each active ingredient is administered sequentially, *i.e.* serially, whereas in combination therapy, effective dosages of two or more active ingredients are administered together.

Metabolites of the Compounds of the Invention

Also falling within the scope of this invention are the *in vivo* metabolic products of the compounds described herein. Such products may result for example from the oxidation, reduction, hydrolysis, amidation, esterification and the like of the administered compound, primarily due to enzymatic processes. Accordingly, the invention includes compounds produced by a process comprising contacting a compound of this invention with a mammal for a period of time sufficient to yield a metabolic product thereof. Such products typically are identified by preparing a radiolabelled (*e.g.*, C^{14} or H^3) compound of the invention, administering it parenterally in a detectable dose (*e.g.*, greater than about 0.5 mg/kg) to an animal such as rat, mouse, guinea pig, monkey, or to man, allowing sufficient time for metabolism to occur (typically about 30 seconds to 30 hours) and isolating its conversion products from the urine, blood or other biological samples. These products are easily isolated since they are labeled (others are isolated by the use of antibodies capable of binding epitopes surviving in the metabolite). The metabolite structures are determined in conventional fashion, *e.g.*, by MS or NMR analysis. In general, analysis of metabolites is done in the same way as conventional drug metabolism studies well-known to those skilled in the art. The conversion products, so long as they are not otherwise found *in vivo*, are useful in diagnostic assays for therapeutic dosing of the compounds of the invention even if they possess no antiviral activity of their own.

Methods for determining stability of compounds in surrogate gastrointestinal secretions are known. Compounds are defined herein as stable in the gastrointestinal tract where less than about 50 mole percent of the protected groups are deprotected in surrogate intestinal or gastric juice upon incubation for 1 hour at 37 °C. Simply because the compounds are stable to the

gastrointestinal tract does not mean that they cannot be hydrolyzed *in vivo*. The phosphonate prodrugs of the invention typically will be stable in the digestive system but are substantially hydrolyzed to the parental drug in the digestive lumen, liver or other metabolic organ, or within cells in general.

Antiviral Activity

Another aspect of the invention relates to methods of inhibiting viral infections, comprising the step of treating a sample or subject suspected of needing such inhibition with a composition of the invention.

Within the context of the invention samples suspected of containing a virus include natural or man-made materials such as living organisms; tissue or cell cultures; biological samples such as biological material samples (blood, serum, urine, cerebrospinal fluid, tears, sputum, saliva, tissue samples, and the like); laboratory samples; food, water, or air samples; bioproduct samples such as extracts of cells, particularly recombinant cells synthesizing a desired glycoprotein; and the like. Typically the sample will be suspected of containing an organism which induces a viral infection, frequently a pathogenic organism such as an tumor virus. Samples can be contained in any medium including water and organic solvent\water mixtures. Samples include living organisms such as humans, and man made materials such as cell cultures.

If desired, the anti-virus activity of a compound of the invention after application of the composition can be observed by any method including direct and indirect methods of detecting such activity. Quantitative, qualitative, and semiquantitative methods of determining such activity are all contemplated. Typically one of the screening methods described above are applied, however, any other method such as observation of the physiological properties of a living organism are also applicable.

The antiviral activity of a compound of the invention can be measured using standard screening protocols that are known. For example, the antiviral activity of a compound can be measured using the following general protocol.

HCV IC_{50} Determination

Assay Protocol: NS5b polymerase assay (40 μL) was assembled by adding 28 μL polymerase mixture (final concentration: 50 mM Tris-HCl at pH 7.5, 10 mM KCL, 5 mM $MgCl_2$, 1 mM DTT, 10 mM EDTA, 4 ng/μL of RNA template, and 75 nM HCV Δ21 NS5b polymerase) to assay plates followed by 4 μL of compound dilution. The polymerase and compound were pre-incubated at 35 °C for 10 minute before the addition of 8 μL of nucleotide substrate mixture (33P-α-labeled competing nucleotide at K_M and 0.5 mM of the remaining three nucleotides). The assay plates were covered and incubated at 35 °C for 90 min. Reactions were then filtered through 96-well DEAE-81 filter plates via vacuum. The filter plates were then washed under vacuum with multiple volumes of 0.125 M $NaHPO_4$, water, and ethanol to remove unincorporated label. Plates were then counted on TopCount to assess the level of product synthesis over background controls. The IC50 value was determined using Prism fitting program

HCV EC_{50} Determination

Replicon cells were seeded in 96-well plates at a density of 8×10^3 cells per well in 100 μL of culture medium, excluding Geneticin. Compound was serially diluted in 100% DMSO and then added to the cells at a 1:200 dilution, achieving a final concentration of 0.5% DMSO and a total volume of 200 μL. Plates were incubated at 37°C for 3 days, after which culture medium was removed and cells were lysed in lysis buffer provided by Promega's luciferase assay system. Following the manufacturer's instruction, 100 μL of luciferase substrate was added to the lysed cells and luciferase activity was measured in a TopCount luminometer.

Typically, compounds of the invention that were tested were found to have an EC_{50} of less than about 1000 μM (Huh7). Some compounds demonstrated an EC_{50} of less than about 250 μM (Huh7).

The cytotoxicity of a compound of the invention can be determined using the following general protocol.

Cytotoxicity Cell Culture Assay (Determination of CC50):

The assay is based on the evaluation of cytotoxic effect of tested compounds using a metabolic substrate.

Assay protocol for determination of CC50:

1. Maintain MT-2 cells in RPMI-1640 medium supplemented with 5% fetal bovine serum and antibiotics.
2. Distribute the cells into a 96-well plate (20,000 cell in 100 µl media per well) and add various concentrations of the tested compound in triplicate (100 µl/well). Include untreated control.
3. Incubate the cells for 5 days at 37 °C.
4. Prepare XTT solution (6 ml per assay plate) in dark at a concentration of 2mg/ml in a phosphate-buffered saline pH 7.4. Heat the solution in a water-bath at 55°C for 5 min. Add 50 µl of N-methylphenazonium methasulfate (5 µg/ml) per 6 ml of XTT solution.
5. Remove 100 µl media from each well on the assay plate and add 100 µl of the XTT substrate solution per well. Incubate at 37 °C for 45 to 60 min in a CO_2 incubator.
6. Add 20 µl of 2% Triton X-100 per well to stop the metabolic conversion of XTT.
7. Read the absorbance at 450 nm with subtracting off the background at 650 nm.
8. Plot the percentage absorbance relative to untreated control and estimate the CC50 value as drug concentration resulting in a 50% inhibition of the cell growth. Consider the absorbance being directly proportional to the cell growth.

Exemplary Methods of Making the Compounds of the Invention.

The invention also relates to methods of making the compounds of the invention. The compounds are prepared by any of the applicable techniques of organic synthesis. Many such techniques are well known in the art. However, many of the known techniques are elaborated in Compendium of Organic Synthetic Methods (John Wiley & Sons, New York), Vol. 1, Ian T. Harrison and

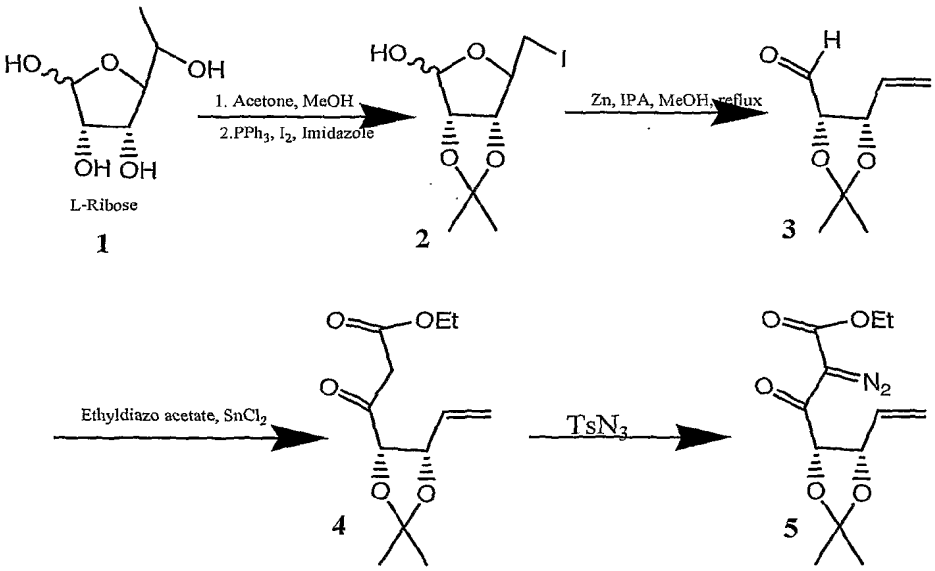
Shuyen Harrison, 1971; Vol. 2, Ian T. Harrison and Shuyen Harrison, 1974; Vol. 3, Louis S. Hegedus and Leroy Wade, 1977; Vol. 4, Leroy G. Wade, jr., 1980; Vol. 5, Leroy G. Wade, Jr., 1984; and Vol. 6, Michael B. Smith; as well as March, J., Advanced Organic Chemistry, Third Edition, (John Wiley & Sons, New York, 1985), Comprehensive Organic Synthesis. Selectivity, Strategy & Efficiency in Modern Organic Chemistry. In 9 Volumes, Barry M. Trost, Editor-in-Chief (Pergamon Press, New York, 1993 printing).

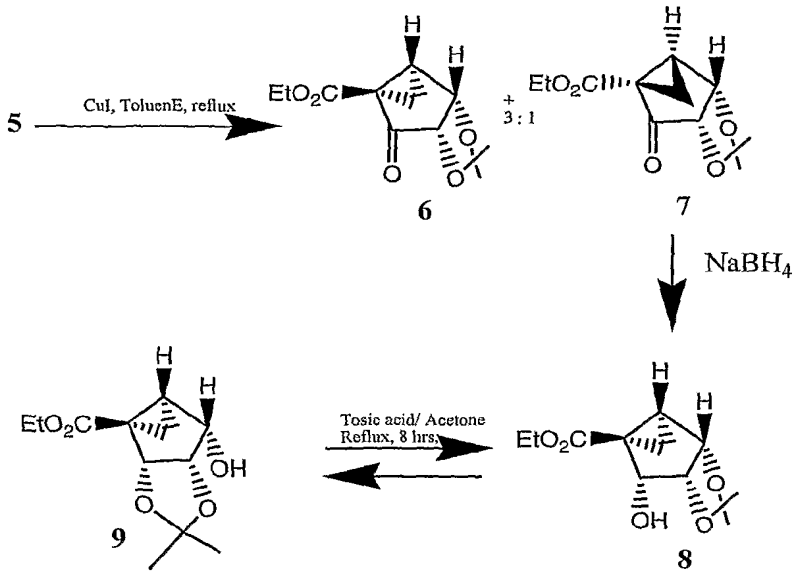
Exemplary methods for the preparation of the compounds of the invention are provided below. These methods are intended to illustrate the nature of such preparations are not intended to limit the scope of applicable methods. Exemplary methods for the preparation of the compounds of the invention are also illustrated in Figures 1-6.

Synthetic intermediates and methods that are useful for preparing compounds of the invention are described by Joshi et al., *J.Org. Chem.*, **2005**, *70*, 439-447; Gallos et al., *Tetrahedron*, **2002**, *58*, 8043-8053; Paquette et al., *J. Org. Chem.*, **1995**, *60*, 7849-7856; and Kim et al., *J. Med. Chem.*, **2002**, **45**, 208-218.

Representative compounds of the invention were prepared as described below.

An intermediate compound **9** was prepared as illustrated below.





L-Ribose **1** was converted into the iodides **2**, which were reductively cleaved with Zn to afford the aldehyde **3**. This aldehyde was unstable and was reacted directly with ethyl diazoacetate to afford keto ester **4**. The keto ester was reacted with tosyl azide to afford the diazo derivative **5**, which underwent a thermally-induced intramolecular cyclopropanation to give the bicyclo[3.1.0]hexan-2-one derivatives **6** and **7** with a diastereoisomeric ratio of (3:1) favoring isomer **6**. The bicyclo derivative **6** was isolated by chromatography and reduced stereospecifically with $NaBH_4$ to give alcohol **8** as a single product in 69% yield. This alcohol **8** was subjected to an acid-catalyzed equilibration to produce the isomeric acetonide **9**, which was isolated in 35% yield by crystallization from cyclohexane. The remaining alcohol **8** was recycled.

Preparation of compounds **2-9**

Ethyl (4*S*,5*S*)-3-[2,2-dimethyl-5-vinyl(1,3-dioxolan-4-yl)]-3-oxopropanoate 4: Concentrated HCl was added to a solution containing L-Ribose **1** (75g, 0.5 mol) in acetone (200 ml) and methanol (200 ml) at room temperature. The resulting reaction mixture was refluxed for 2 hours, cooled to

room temperature, neutralized with pyridine, and concentrated. The residue was partitioned between water (300 ml) and ethyl acetate (300 ml three times); the combined organic phase was washed with saturated solution of copper sulphate, followed by brine, and the resulting solution was dried over sodium sulphate and concentrated. The crude residue was used directly in the next step (82 g).

The crude residue was dissolved in toluene (800 ml) and was added with imidazole (51 g, 0.75 mol), triphenylphosphine (197g, 0.75 mol), and acetonitrile 175 ml). The resulting reaction mixture was heated to 70 °C, and Iodine (131g, 0.5 mol) was added portion wise and carefully till the reaction mixture remained dark brown. The reaction mixture was maintained at 70 °C for 1 hour. The top clear organic layer was decanted; and the residue was washed with toluene (200 ml). The combined organic layer was washed with 5% sodium thiosulphate solution, water, and brine and concentrated. The crude residue was treated with mixture containing hexane and ethyl acetate (3:1). Solid triphenylphosphine oxide separated out, was filtered, and the filtrate was concentrated. Further purification was effected by flash column chromatography, with ethyl acetate and hexane (5: 95) as the eluant, to give the iodo derivative **2** as a mixture of anomers. (95g, 64% in two steps).

Powdered Zn (16.2g, 0.25 mol) was added to the solution containing the iodides **2** (15.7 g, 0.05 mol) in methanol (25ml) and isopropanol (75 ml). The resulting reaction mixture was allowed to reflux for 1 hour and was cooled at room temperature. The solution was decanted and concentrated (under reduced pressure). The residue was treated with water (100 ml) containing 5% acetic acid, extracted with dichloromethane (100 ml) , dried, and concentrated under reduced pressure to give the crude aldehyde **3** (7 g).

Aldehyde **3** (7 g) in dichloromethane (40 ml) was treated with $SnCl_4$ (3.8g, 0.02 mol) and ethyldiazoacetate (7.6 g, 0.04 mol) at 0 °C, and the mixture was allowed to stir at room temperature for 8 hours. The mixture was filtered through a pad of celite, concentrated, and purified by column chromatography (silica gel, hexane: ethylacetate, 95:5) to afford **4**, (5g, 42% based on the iodide derivative) as an oil. ^1H NMR ($CDCl_3$) δ 12.08 (s, 0.1 H, D_2O exchangeable, enolic O*H*), 5.92-6.06 (m, 1 H), 5.37-5.56 (m, 2 H), 4.46-4.62 (m, 1 H), 4.18-

4.38 (m, 3 H), 3.75 (AB q, 2 H, J = 16.4 Hz), 1.54-1.57 (m, 6 H, 2), 1.34-1.41 (m, 3 H); FAB MS *m/z* (relative intensity) 185 (7.2), 243 (MH^+, 2).

Ethyl (4*S*,5*S*)-3-[2,2-dimethyl-5-vinyl(1,3-dioxolan-4-yl)]-2-diazo-3-oxopropanoate 5. To a stirred solution of keto ester **4** (9.68 g, 0.04 mol) in acetonitrile (40 mL) was successively added tosyl azide (8.26 g, 0.042mol) and Et_3N (8.8 g, 80 mmol). The resulting reaction mixture was concentrated after stirring for 1 hour at room temperature The diazo derivative was directly purified by column chromatography (silica gel; hexanes:EtOAc, 90:10) to furnish **5** (7.5 g, 70%) as an oil ^1H NMR ($CDCl_3$) δ 5.79(ddd, 1 H, J = 17.3, 10.1, 7.3 Hz), 5.70 (d, 1 H, J = 7.6 Hz), 5.45 (d, 1 H, J = 17.1 Hz), 5.33 (d, 1 H, J = 10.2 Hz), 5.07 (t, 1 H, J = 7.5 Hz), 4.34 (q, 2 H, J = 7.1 Hz), 1.74 (s, 3 H), 1.51 (s, 3 H), 1.41 (t, 3 H, J = 7.1 Hz); FAB MS *m/z* (relative intensity) 269 (MH^+, 86).

Ethyl (1*S*,3*S*,4*S*,5*S*)-3,4-*O*-isopropylidene-2-oxobicyclo[3.1.0]-hexanecarboxylate 6. To a stirred solution of diazo compound **5** (5.36 g, 20 mmol) in dry toluene (30 mL) was added CuI (0.190 g, 1 mmol) at room temperature. The reaction mixture was refluxed for 8 hours, cooled to room temperature, concentrated, and purified by column chromatography (silica gel; hexanes:EtOAc, 75:25) to provide bicylic compound **6** (1.72 g, 36%) and compound **7** (0.57 g, 12%). Compound **6**: ^1H NMR ($CDCl_3$) δ 5.13 (ddd, 1 H, J = 8.3, 5.4, 1.0 Hz), 4.39 (d, 1 H, J = 8.3 Hz), 4.29 (q, 2 H, J = 7.1 Hz), 2.84 (dt, 1 H, J = 8.3, 5.3 Hz), 2.18 (dd, 1 H, J = 8.1, 5.1 Hz), 1.89 (t, 1 H, J ~ 5.2 Hz), 1.59 (s, 3 H), 1.39 (s, 3 H), 1.36 (t, 3 H, J = 7.1 Hz); FAB MS *m/z* (relative intensity) 241 (MH^+, 100). **7**: ^1H NMR ($CDCl_3$) δ 4.81 (d, 1 H, J = 5.1 Hz), 4.38 (dd, 1 H, J = 4.8, 1.7 Hz), 4.32 (dq, 2 H, J = 7.1, 1.5 Hz), 2.96 (dd, 1 H, J = 8.7, 5.7 Hz), 2.21 (ddd, 1 H, J = 8.8, 5.7, 1.7 Hz), 1.53 (s, 3 H), 1.45 (s, 3 H), 1.37 (t, 3 H, J = 4.1 Hz), 1.35 (irregular t, 1 H); FAB MS m/z (relative intensity) 241 (MH^+, 100).

Ethyl (1*S*,2*R*,3*S*,4*S*,5*S*)-3,4-*O*-isopropylidene-2-hydroxybicyclo[3.1.0]-hexane-carboxylate (8). To a stirred solution of compound **6** (2.4 g, 10 mmol) in ethanol (20 mL) at room temperature was added $NaBH_4$ (0.38 g, 5 mmol) and stirring was continued for an additional 1 hour. The reaction mixture was treated with acetone (2 mL) and concentrated to dryness. The residue was purified by column chromatography (silica gel; hexanes:EtOAc, 70:30) to give compound **8**

(1.68g, 69%) as a white solid; m.p.109 ^{0}C (cyclohexane); ^{1}H NMR ($CDCl_3$) δ 4.95 (t, 1 H, J = 7.5 Hz), 4.88 (t, 1 H, J = 6 Hz), 4.60 (t, 1 H, J = 7 Hz), 4.12-4.24, (m, 2 H), 2.48 (d, 1 H, J = 12 Hz, OH), 2.16-2.26 (m, 1 H), 1.48-1.61 (m, 5 H), 1.32 (s, 3 H), 1.26 (t, 3 H, J = 6.5 Hz). FAB MS *m/z* (relative intensity) 243 (MH^+, 100).

Ethyl (1*S*,2*R*,3*S*,4*S*,5*S*)-2,3-*O*-(isopropylidene)-4-hydroxybicyclo[3.1.0]-hexane-carboxylate 9. A solution of compound **8** (0.96 g, 4.0 mmol) and *p*-TsOH•H_2O (0.38 g, 2 mmol) in acetone (20 mL) was refluxed for 8 hours. Following the addition of NEt_3 (2 mL), the solution was concentrated under reduced pressure. Flash column chromatography (silica gel; $CHCl_3$:MeOH, 9:1) of the residue furnished a mixture of isomerized alcohols **8** and **9** in a 6:4 ratio based on NMR. This crude mixture was further purified by careful crystallization from cyclohexane to obtain pure **9** (0.340 g, 35%) as colorless crystals. The remaining alcohol **8** was recycled. *Compound* **9**: ^{1}H NMR ($CDCl_3$) δ 5.38 (d, 1 H, J = 5.5 Hz), 4.42-4.64 (m, 2 H), 4.08-4.21 (m, 2 H), 2.39-2.45 (m, 2 H), 1.42-1.62 (m, 5 H), 1.35 (s, 3 H), 1.12 (t, 2 H, J = 3.2 Hz); FAB MS *m/z* (relative intensity) 243.1 (MH^+, 100).

As described in Examples **1-6** representative compounds of the invention were prepared from Compound **9** as illustrated in Figure 1. Alcohol **9** was subjected to a Mitsunobu coupling conditions using variety of purine bases **10-16** to afford the condensed products **17-22**. Reduction with DIBAL-H afforded compounds **23-28**. The chloro functionality was substituted with an amino group to afford compounds **29-34**. The final hydrolysis of the isopropylidene group using 10% TFA in MeOH at 70 ^{O}C afforded compounds **35-40**, which are compounds of formula I.

Examples 1-6

The following general procedure was used to prepare the compounds of Examples **1-6**.

A mixture containing an isopropylidene analog **29-34** (0.04 mmol), 10% trifluoroacetic acid /MeOH (5 mL), and H_2O (0.5 mL) was heated at 70 °C for 3 hours. The solvent was removed and the residue was dried by coevaporation

with toluene. The residue was purified using preparative TLC ($CHCl_3$:MeOH, 9:1) to afford the title compound **35-40** as a colorless solid in 62-67% yields.

Example 1 **(1'*S*,2'*R*,3'*S*,4'*R*,5'*S*)-4-(6-amino-2-chloro-purin-9-yl)-1-[hydroxymethyl]bicyclo[3.1.0]hexane-2,3-diol 35.** ^{1}H NMR (CD_3OD, 300 MHz) δ 0.71-0.78 (m, 1H), 1.50-1.64 (m, 2H), 3.85 (d, J = 6.9, Hz, 1H), 3.25 (d, J = 12, Hz, 1H), 4.75 (dd, J = 1.5, 1.5 Hz 1H), 4.76-4.79 (m, 2H), 8.49 (s, 1H). HRMS $(M + 1)^+$: calculated 312.0863, found 312.0871.

Example 2 **(1'*S*,2'*R*,3'*S*,4'*R*,5'*S*)-4-(6-amino-2-iodo-purin-9-yl)-1-[hydroxymethyl]bicyclo[3.1.0]hexane-2,3-diol 36.** ^{1}H NMR (CD_3OD, 300 MHz) δ 0.72-0.78 (m, 1H), 1.51-1.62 (m, 2H), 3.33-3.37 (m, 1H), 3.86 (d, J = 6.6, Hz, 1H), 4.25 (d, J = 13.5, Hz 1H), 4.76-4.79 (m, 2H), 8.42 (s, 1H). HRMS $(M + 1)^+$: calculated 404.0220, found 404.0204.

Example 3 **(1'*S*,2'*R*,3'*S*,4'*R*,5'*S*)-4-(6-amino-2-fluoro-purin-9-yl)-1-[hydroxymethyl]bicyclo[3.1.0]hexane-2,3-diol 37.** ^{1}H NMR (CD_3OD, 300 MHz) δ 0.72-0.76 (m, 1H), 1.51-1.63 (m, 2H), 3.33-3.37 (m, 1H), 3.85 (d, J = 6.9, Hz, 1H), 4.24 (d, J = 12, Hz 1H), 4.76-4.79 (m, 2H), 8.45 (s, 1H). HRMS $(M + 1)^+$: calculated 296.1159, found 296.1162.

Example 4 **(1'*S*,2'*R*,3'*S*,4'*R*,5'*S*)-4-(6-amino-2-methylthio-purin-9-yl)-1-[hydroxymethyl]bicyclo[3.1.0]hexane-2,3-diol 38.** ^{1}H NMR (CD_3OD, 300 MHz) δ 0.72-0.78 (m, 1H), 1.52-1.63 (m, 2H), 2.57 (s, 3H), 3.43-3.56 (m, 1H), 3.85-3.92 (m, 1H), 4.25 (d, J = 11.4, Hz, 1H), 4.76-4.79 (m, 2H), 8.41 (s, 1H). HRMS $(M + 1)^+$: calculated 324.1130, found 324.1120.

Example 5 **(1'*S*,2'*R*,3'*S*,4'*R*,5'*S*)-4-(6-amino-purin-9-yl)-1-[hydroxymethyl]bicyclo[3.1.0]hexane-2,3-diol 39.** ^{1}H NMR (CD_3OD, 300 MHz) δ 0.73-0.79 (m, 1H), 1.52-1.66 (m, 2H), 3.28-3.33 (m, 1H), 3.88 (d, J = 3.6, Hz, 1H), 4.26 (d, J = 12, Hz, 1H), 4.76-4.79 (m, 2H), 8.20 (s, 1H), 8.51 (s, 1H). HRMS $(M + 1)^+$: calculated 278.1253, found 278.1252.

Example 6 **(1'*S*,2'*R*,3'*S*,4'*R*,5'*S*)-4-(4-amino-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-1-[hydroxymethyl]bicyclo[3.1.0]hexane-2,3-diol 40.** ^{1}H NMR (CD_3OD, 300 MHz) δ 0.66-0.74 (m, 1H), 1.48-1.58 (m, 2H), 3.28-3.33 (m, 1H), 3.76 (d, J = 6.9, Hz, 1H), 4.26 (d, J = 10.8, Hz, 1H), 4.75 (d, J = 6.6, Hz, 1H), 4.97 (s, 1H), 6.57-6.58 (m, 1H), 7.45 (s, 1H), 8.12 (s, 1H). HRMS $(M + 1)^+$: calculated 277.1301, found 277.1283.

The starting isopropylidene analogs **29-34** used in Examples 1-6 were prepared as follows.

Examples 1a-6a

The following general procedure was used for the Mitsunobu coupling reaction of nucleoside purine bases **10-16** and the sugar moiety **9**.

A mixture of triphenyl phosphine (0.104 g, 0.4 mmol), and the substituted purine **10-16** (0.4 mmol) in dry THF (2 mL) was treated with diisopropylazodicarboxylate (0.080 g, 0.4 mmol) at room temperature. After 20 minutes stirring, a solution of sugar **9** (0.048 g, 0.2 mmol) in THF (1 mL) was added and the mixture was stirred further for 8 hours. Concentration and purification of the residue by column chromatography (silica gel; Ethylacetate:-Hexane, 3:1) provided nucleoside ester analogues **17-22** in 35% to 42 % yields.

Example 1a **Ethyl (1'*S*,2'*R*,3'*S*,4'*R*,5'*S*)-4'-(2,6-dichloropurin-9-yl]-2',3'-*O*-(isopropylidene)-bicyclo[3.1.0]hexanecarboxylate 17.** Compound **17** was obtained from 2,6-dichloro purine **10**. ^{1}H NMR ($CDCl_3$) δ 8.09 (s, 1 H), 5.85 (d, 1 H, 6.5 Hz), 4.91 (s, 1 H), 4.72 (d, 1 H, J = 5.5 Hz), 4.05-4.38 (m, 2 H), 2.14-2.2 (m, 1 H), 1.75-1.82 (m, 1 H), 1.52-1.62 (m, 4 H), 1.15-1.38 (m, 6 H); FAB MS *m/z* (relative intensity) 413.1 (MH^+, 100).

Example 2a **(1'*S*,2'*R*,3'*S*,4'*S*,5'*S*)-4'-[6-Chloro-2-iodopurin-9-yl]-2',3'-isopropylidenebicyclo[3.1.0]hexane-1'-carboxylic Acid Ethyl Ester 18.** Compound **18** was obtained from 2-iodo-6-chloro-purine **11**. ^{1}H NMR ($CDCl_3$, 300 MHz) δ1.30-1.36 (m, 4H), 1.57 (s, 6H), 1.75-1.80 (m, 1H), 2.12-2.22 (m,

1H), 4.1-4.2 (m, 2H), 4.75 (d, J = 14 Hz, 1H), 4.92 (s, 1H), 5.85 (d, J = 15 Hz, 1H), 7.98 (s, 1H). MS (*m/e*) (positive-FAB) 505.0 $(M + 1)^+$.

Example 3a **(1'*S*,2'*R*,3'*S*,4'*S*,5'*S*)-4'-[6-Chloro-2-fluoropurin-9-yl]-2',3'-isopropylidenebicyclo[3.1.0]hexane-1'-carboxylic Acid Ethyl Ester 19.** Compound **19** was obtained from 2-fluoro-6-chloro-purine **12**. ^{1}H NMR ($CDCl_3$, 300 MHz) δ1.23-1.36 (m, 4H), 1.55 (s, 6H), 1.76-1.82 (m, 1H), 2.42-2.46 (m, 1H), 4.14-4.28 (m, 2H), 4.73 (d, J = 10 Hz, 1H), 4.93 (s, 1H), 5.88 (d, J = 7 Hz, 1H), 8.07 (s, 1H). HRMS $(M + 1)^+$: calculated 397.1079, found 397.1083.

Example 4a **(1'*S*,2'*R*,3'*S*,4'*S*,5'*S*)-4'-[6-Chloro-2-methylthiopurin-9-yl]-2',3'-isopropylidenebicyclo[3.1.0]hexane-1'-carboxylic Acid Ethyl Ester 20.** Compound **20** was obtained from 2-methylthio-6-chloro purine **13**. ^{1}H NMR ($CDCl_3$, 300 MHz) δ1.25-1.55 (m, 4H), 1.56 (s, 6H), 1.75-1.82 (m, 1H), 2.25-2.32 (m, 1H), 2.64 (s, 3H), 4.18-4.29 (m, 2H), 4.82 (d, J = 12 Hz, 1H), 4.92 (s, 1H), 5.85 (d, J = 11 Hz, 1H), 7.90 (s, 1H). MS (*m/e*) (positive-FAB) 425.10 $(M + 1)^+$.

Example 5a **(1'*S*,2'*R*,3'*S*,4'*S*,5'*S*)-4'-[6-Chloropurin-9-yl]-2',3'-isopropylidenebicyclo[3.1.0]hexane-1'-carboxylic Acid Ethyl Ester 21.** Compound **21** was obtained from 6-chloropurine **15**. ^{1}H NMR ($CDCl_3$, 300 MHz) δ1.26-1.57 (m, 4H), 1.59 (s, 6H), 1.75-1.8 (m, 1H), 2.24-2.32 (m, 1H), 4.12-4.38 (m, 2H), 4.76 (d, J = 8 Hz, 1H), 5.08 (s, 1H), 5.89 (d, J = 7 Hz, 1H), 8.10 (s, 1H), 8.71 (s, 1H). HRMS $(M + 1)^+$: calculated 379.1173, found 379.1188.

Example 6a **(1'*S*,2'*R*,3'*S*,4'*S*,5'*S*)-4'-[4-chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl]-2',3'-isopropylidenebicyclo[3.1.0]hexane-1'-carboxylic Acid Ethyl Ester 22.** Compound **22** was obtained from 4-chloro-7H-pyrrolo[2,3-d]pyrimidine **16**. ^{1}H NMR ($CDCl_3$, 300 MHz) δ1.22-1.38 (m, 4H), 1.56 (s, 3H), 1.59 (s, 3H) 1.76-1.80 (m, 1H), 2.18-2.26 (m, 1H), 4.14-4.23 (m, 2H), 4.69 (d, J = 8 Hz, 1H), 5.05 (s, 1H), 5.83 (d, J = 8Hz, 1H), 6.64 (s, 1H), 7.15 (d, J = 3.6Hz, 1H), 8.60 (s, 1H) . HRMS $(M + 1)^+$: calculated 378.1221, found 378.1245.

Examples 1b-6b

The following general procedure was used for the DIBAL-H reduction of esters **17-22.**

A stirred solution of ester **17-22** (0.5 mmol) in toluene (10 mL) was cooled to –78 °C and treated dropwise with diisobutylaluminum hydride (DIBAL-H, 1 mL, 1.5 M solution in THF). After 1 hour, methanol (1.5 mL) and 1 M cold sulfuric acid (10 ml) (pH = 4), were added carefully. The reaction mixture was filtered through a pad of Celite and the filtrate was collected, separated, and the aqueous phase was extracted with dichloromethane. The combined organic layer was evaporated and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography ($CHCl_3$:MeOH, 10:1) to give the corresponding alcohols **23-28** in 35 to 56 % yields.

Example 1b **(1'*S*,2'*R*,3'*S*,4'*R*,5'*S*)-4-(2,6-dichloro-purin-9-yl)-1-[hydroxymethyl]bicyclo[3.1.0]hexane-2,3-(*O*-isopropylidine) 23.** ^{1}H NMR ($CDCl_3$, 300 MHz) 51.05-1.08 (m, 1H), 1.21-138 (m, 7H), 1.70-1.74 (m, 1H), 3.51(d, J = 12Hz, 1H), 4.21-4.27 (m, 1H), 4.63 (d, J = 7.5Hz, 1H), 4.96 (s, 1H), 5.51 (d, J = 12Hz, 1H), 8.32 (s, 1H). HRMS $(M + 1)^+$: calculated 371.0678, found 371.0669.

Example 2b **(1'*S*,2'*R*,3'*S*,4'*R*,5'*S*)-4-(6-chloro-2-iodo-purin-9-yl)-1-[hydroxymethyl]bicyclo[3.1.0]hexane-2,3-(*O*-isopropylidine) 24.** ^{1}H NMR ($CDCl_3$, 300 MHz) 51.02-1.05 (m, 1H), 1.21-42 (m, 7H), 1.66-1.71 (m, 1H), 3.60 (d, J = 12Hz, 1H), 4.16(d, J = 12Hz, 1H), 4.65(d, J = 7.2Hz, 1H), 4.97 (s, 1H), 5.47 (d, J = 7.5Hz, 1H), 8.28 (s, 1H). HRMS $(M + 1)^+$: calculated 463.0034, found 463.0021.

Example 3b **(1'*S*,2'*R*,3'*S*,4'*R*,5'*S*)-4-(6-chloro-2-fluoro-purin-9-yl)-1-[hydroxymethyl]bicyclo[3.1.0]hexane-2,3-(*O*-isopropylidine) 25.** ^{1}H NMR ($CDCl_3$, 300 MHz) 51.01-1.09 (m, 2H), 1.25 (s, 6H), 1.66-1.74 (m, 1H), 3.50 (d, J = 11Hz, 1H), 4.18-4.23(m, 1H), 4.62(d, J = 4.8Hz, 1H), 4.95 (s, 1H), 5.48 (dd,

J = 1.5, 1.6Hz, 1H), 8.35 (s, 1H). HRMS $(M + 1)^+$: calculated 355.0973, found 355.0971.

Example 4b **(1'*S*,2'*R*,3'*S*,4'*R*,5'*S*)-4-(6-chloro-2-methythio-purin-9-yl)-1-[hydroxymethyl]bicyclo[3.1.0]hexane-2,3-(*O*-isopropylidine) 26.** HRMS $(M + 1)^+$: calculated 383.0945, found 383.0958.

Example 5b **(1'*S*,2'*R*,3'*S*,4'*R*,5'*S*)-4-(6-chloropurin-9-yl)-1-[hydroxymethyl]bicyclo[3.1.0]hexane-2,3-(*O*-isopropylidine) 27.** HRMS $(M + 1)^+$: calculated 337.1067, found 337.1069.

Example 6b **(1'*S*,2'*R*,3'*S*,4'*R*,5'*S*)-4-(4-chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-1-[hydroxymethyl]bicyclo[3.1.0]hexane-2,3-(*O*-isopropylidine) 28.** HRMS $(M + 1)^+$: calculated 336.1115, found 336.1115.

Examples 1c-6c

The following general procedures were used to convert the chloro group in analogs **23-28** to the corresponding amine. The chloro analog was added to a 20 fold excess of 2M NH_3 in THF and the resulting mixture was stirred at room temperature for 16 hours. Alternatively, the chloro analog was added to a 20 fold excess of saturated ammonia in ethanol and the resulting mixture was stirred at 95 ^oC under pressure in a sealed vessel for 16 hours. Using the above procedures compounds **29-34** were obtained in 60 to 65 % yields.

Example 1c **(1'*S*,2'*R*,3'*S*,4'*R*,5'*S*)-4-(6-amino-2-chloro-purin-9-yl)-1-[hydroxymethyl]bicyclo[3.1.0]hexane-2,3-(*O*-isopropylidine) 29.** HRMS $(M + 1)^+$: calculated 352.1176, found 353.1163.

Example 2c **(1'*S*,2'*R*,3'*S*,4'*R*,5'*S*)-4-(6-amino-2-iodo-purin-9-yl)-1-[hydroxymethyl]bicyclo[3.1.0]hexane-2,3-(*O*-isopropylidine) 30.** HRMS $(M + 1)^+$: calculated 444.0533, found 444.0522

Example 3c **(1'*S*,2'*R*,3'*S*,4'*R*,5'*S*)-4-(6-amino-2-fluoro-purin-9-yl)-1-[hydroxymethyl]bicyclo[3.1.0]hexane-2,3-(*O*-isopropylidine) 31.** HRMS $(M + 1)^+$: calculated 336.1472, found 336.1474.

Example 4c **(1'*S*,2'*R*,3'*S*,4'*R*,5'*S*)-4-(6-amino-2-methylthiopurine-9-yl)-1-[hydroxymethyl]bicyclo[3.1.0]hexane-2,3-(*O*-isopropylidine) 32.** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.94-0.99 (m, 1H), 1.13-1.17 (m, 1H), 1.28 (s, 3H), 1.55 (s, 3H), 1.67-1.71 (m, 1H), 2.59 (s, 3H), 3.33 (dd, J = 2.1, 2.1 Hz, 1H), 3.86 (dd, J = 2.4, 2.4 Hz, 1H), 4.22-4.26 (m, 1H), 4.71-4.75 (m, 2H), 5.55-5.61 (m, 2H), 7.72 (s, 1H). HRMS $(M + 1)^+$: calculated 364.1443, found 364.1447.

Example 5c **(1'*S*,2'*R*,3'*S*,4'*R*,5'*S*)-4-(6-amino-purine-9-yl)-1-[hydroxymethyl]bicyclo[3.1.0]hexane-2,3-(*O*-isopropylidine) 33.** ^{1}H NMR (CD_3OD, 300 MHz) δ 0.95-1.10 (m, 1H), 1.14-1.19 (m, 1H), 1.24 (s, 3H), 1.51 (s, 3H), 1.67-1.78 (m, 1H), 3.44 (d, J = 5.7 Hz, 1H), 4.06 (d, J = 11 Hz, 1H), 4.66 (d, J = 4.2 Hz, 1H), 5.02 (s, 1H), 5.40 (d, J = 7.2 Hz, 1H), 8.19 (s, 1H), 8.31 (s, 1H). HRMS $(M + 1)^+$: calculated 318.1566, found 318.1575.

Example 6c **(1'*S*,2'*R*,3'*S*,4'*R*,5'*S*)-4-(4-amino-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-1-[hydroxymethyl]bicyclo[3.1.0]hexane-2,3-(*O*-isopropylidine) 34.** HRMS $(M + 1)^+$: calculated 317.1614, found 317.1615.

Example 7 The following illustrate representative pharmaceutical dosage forms, containing a compound of formula I or II ('Compound X'), for therapeutic or prophylactic use in humans.

(i) Tablet 1	mg/tablet
Compound X=	100.0
Lactose	77.5
Povidone	15.0
Croscarmellose sodium	12.0
Microcrystalline cellulose	92.5
Magnesium stearate	3.0
	300.0

(ii) Tablet 2	mg/tablet
Compound X=	20.0
Microcrystalline cellulose	410.0
Starch	50.0
Sodium starch glycolate	15.0
Magnesium stearate	5.0
	500.0

(iii) Capsule	mg/capsule
Compound X=	10.0
Colloidal silicon dioxide	1.5
Lactose	465.5
Pregelatinized starch	120.0
Magnesium stearate	3.0
	600.0

(iv) Injection 1 (1 mg/ml)	mg/ml
Compound X= (free acid form)	1.0
Dibasic sodium phosphate	12.0
Monobasic sodium phosphate	0.7
Sodium chloride	4.5
1.0 N Sodium hydroxide solution (pH adjustment to 7.0-7.5)	q.s.
Water for injection	q.s. ad 1 mL

(v) Injection 2 (10 mg/ml)	mg/ml
Compound X= (free acid form)	10.0
Monobasic sodium phosphate	0.3
Dibasic sodium phosphate	1.1
Polyethylene glycol 400	200.0
01 N Sodium hydroxide solution (pH adjustment to 7.0-7.5)	q.s.
Water for injection	q.s. ad 1 mL

(vi) Aerosol	mg/can
Compound X=	20.0
Oleic acid	10.0
Trichloromonofluoromethane	5,000.0
Dichlorodifluoromethane	10,000.0
Dichlorotetrafluoroethane	5,000.0

The above formulations may be obtained by conventional procedures well known in the pharmaceutical art.

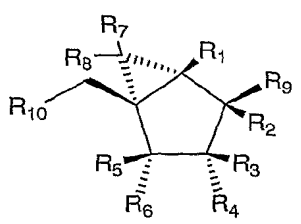
All publications, patents, and patent documents cited hereinabove are incorporated by reference herein, as though individually incorporated by reference. The invention has been described with reference to various specific

and preferred embodiments and techniques. However, it should be understood that many variations and modifications may be made while remaining within the spirit and scope of the invention.

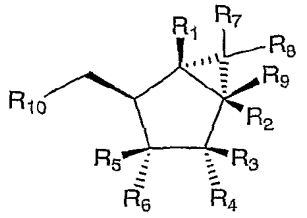
Claims

We claim:

1. A compound of formula I or II:



(I)



(II)

wherein:

R_1 is H, halo, OR_a, SR_a, or NR_bR_c;

R_2 is H, halo, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, or $(C_2\text{-}C_6)$alkynyl;

R_3 is H, halo, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, or $(C_2\text{-}C_6)$alkynyl; and R_4 is H, halo, azido, cyano, nitro, OR_a, SR_a, NR_bR_c, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, or $(C_2\text{-}C_6)$alkynyl; or R_3 and R_4 taken together are =O, $=NR_d$, $=CR_fR_g$; or R_3 and R_4 taken together with the carbon atom to which they are attached form a 3-7 membered carbocyclic ring wherein one carbon atom can optionally be replaced with -O-, -S-, or $-NR_a$-;

R_5 is H, halo, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, or $(C_2\text{-}C_6)$alkynyl; and R_6 is H, halo, azido, cyano, nitro, OR_a, SR_a, NR_bR_c, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, or $(C_2\text{-}C_6)$alkynyl; or R_5 and R_6 taken together are =O, $=NR_d$, $=CR_fR_g$; or R_5 and R_6 taken together with the carbon atom to which they are attached form a 3-7 membered carbocyclic ring wherein one carbon atom can optionally be replaced with -O-, -S-, or $-NR_a$-;

R_7 and R_8 are each independently H or halo;

R_9 is a nucleoside base;

R_{10} is OH, $-OP(=O)(OH)_2$, $-OP(=O)(OH)-P(=O)(OH)_2$, $-OP(=O)(OH)-P(=O)(OH)-P(=O)(OH)_2$, or a phosphonate;

each R_a is independently H, $(C_1\text{-}C_6)$alkyl, or $(C_1\text{-}C_6)$alkanoyl;

each R_b and R_c is independently H, $(C_1\text{-}C_6)$alkyl, or $(C_1\text{-}C_6)$alkanoyl;

each R_d is independently H, $(C_1\text{-}C_6)$alkyl, or OH;

each R_e is independently H or (C_1-C_6)alkyl; and

each R_f and R_g is independently H, (C_1-C_6)alkyl, or halo;

wherein each (C_1-C_6)*alkyl*, (C_2-C_6)*alkenyl*, or (C_2-C_6)*alkynyl of* R_2-R_6 and R_a-R_g is optionally substituted with one or more halo, hydroxy, or (C_1-C_6)alkoxy;

or a pharmaceutically acceptable salt or prodrug thereof;

provided the compound is not (1'*S*,2'*R*,3'*S*,4'*R*,5'*S*)-4-(6-amino-purin-9-yl)-1-[hydroxymethyl]bicyclo[3.1.0]hexane-2,3-diol; and

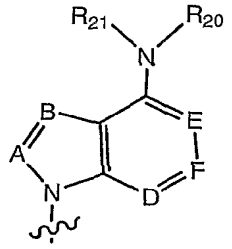
provided the compound is not (1'*S*,2'*R*,3'*S*,4'*R*,5'*S*)-4-(6-amino-9H-purin-9-yl)-1-[phosphoryloxymethyl]bi-cyclo[3.1.0]hexane-2,3-diol; 5-(6-amino-9H-purin-9-yl)-1-[phosphoryloxymethyl]bicyclo[3.1.0]hexane-2,3-diol; 5-(6-amino-9H-purin-9-yl)-1-[hydoxymethyl]bicyclo[3.1.0]hexane-2,3-diol; (1'*S*,2'*R*,3'*S*,4'*R*,5'*S*)-4-(6-amino-9H-purin-9-yl)-1-[triphosphoryloxymethyl]bi-cyclo[3.1.0]hexane-2,3-diol; 5-(6-amino-9H-purin-9-yl)-1-[triphosphoryloxymethyl]bicyclo[3.1.0]hexane-2,3-diol; (1'*S*,2'*R*,3'*S*,4'*R*,5'*S*)-4-(2,4(*H*,3*H*)-dioxopyrimidin-1-yl)-1-(phosphoryloxymethyl)bi-cyclo[3.1.0]hexane-2,3-diol; (1'*S*,2'*R*,3'*S*,4'*R*,5'*S*)-4-(2,4(*H*,3*H*)-dioxopyrimidin-1-yl)-1- (diphosphoryloxymethyl)bicyclo[3.1.0]hexane-2,3-diol; or (1'*S*,2'*R*,3'*S*,4'*R*,5'*S*)-4-(2,4(H,3H)-dioxopyrimidin-1-yl)-1-(triphosphoryloxymethyl)bicyclo[3.1.0]hexane-2,3-diol.

2. The compound of claim 1 wherein R_1 is H; R_2 is H; R_3 is H; R_4 is H or OH; R_5 is H; and R_6 is OH.

3. The compound of claim 1 wherein R_7 and R_8 are each H.

4. The compound of claim 1 wherein R_9 is a heterocycle or a substituted heterocycle.

5. The compound of claim 1 wherein R_9 has the following formula:



wherein:

R_{20} is OH or (C_1-C_6)alkoxy that is optionally substituted with one or more R_{22}; and R_{21} is H or (C_1-C_6)alkyl that is optionally substituted with one or more R_{22}; or R_{20} and R_{21} together with the nitrogen to which they are attached form a heterocyclic ring that is optionally subsitituted with one or more R_{22};

each R_{22} is independently (C_1-C_6)alkyl, (C_1-C_6)alkylthio, (C_1-C_6)alkoxy, (C_1-C_6)alkanoyl, (C_1-C_6)alkanoyloxy, (C_1-C_6)alkoxycarbonyl, $NR_{23}R_{24}$, -C(=O)$NR_{23}R_{24}$, aryl, heteroaryl, cyano, halo, hydroxy, nitro, carboxy, or (C_3-C_8)cycloalkyl;

R_{23} and R_{24} are each independently H, (C_1-C_6)alkyl or (C_1-C_6)alkanoyl;

wherein each aryl or heteroaryl of R_{22} is optionally substituted with one or more (C_1-C_6)alkyl, (C_1-C_6)alkylthio, (C_1-C_6)alkoxy, (C_1-C_6)alkanoyl, (C_1-C_6)alkanoyloxy, (C_1-C_6)alkoxycarbonyl, $NR_{23}R_{24}$, -C(=O)$NR_{23}R_{24}$, cyano, halo, hydroxy, nitro, carboxy, (C_3-C_8)cycloalkyl, trifluoromethoxy, mercapto, or trifluoromethyl; and

A, B, D, F, and E are each independently >N or >C-R_{25};

each R_{25} is independently H, cyano, nitro, (C_1-C_6)alkyl, (C_1-C_6)alkenyl, (C_1-C_6)alkynyl, -$NHCONH_2$, C(=O)$NR_{26}R_{27}$, $COOR_{28}$, hydroxy, (C_1-C_6)alkoxy, -$NR_{26}R_{27}$, halo, 1,3-oxazol-2-yl, 1,3-oxazol-5-yl, 1,3-thiazol-2-yl, imidazol-2-yl, 2-oxo-[1,3]dithiol-4-yl, furan-2-yl, or 2H-[1,2,3]triazol-4-yl;

each R_{26} and R_{27} is independently H, (C_1-C_6)alkyl, (C_1-C_6)alkenyl, (C_1-C_6)alkynyl, (C_3-C_8)cycloalkyl, aryl, heterocycle, hydroxy, or (C_1-C_6)alkoxy; or R_{26} and R_{27} together with the nitrogen to which they are attached form a heterocycle; and

each R_{28} is independently H, (C_1-C_6)alkyl, (C_1-C_6)alkenyl, (C_1-C_6)alkynyl, (C_3-C_8)cycloalkyl, aryl, or heterocycle;

wherein each (C_1-C_6)alkyl, (C_1-C_6)alkenyl, (C_1-C_6)alkynyl, (C_3-C_8)cycloalkyl, aryl, heterocycle, and (C_1-C_6)alkoxy of R_{26} and R_{27} is optionally

substituted with one or more (C_1-C_6)alkyl, (C_1-C_6)alkylthio, (C_1-C_6)alkoxy, (C_1-C_6)alkanoyl, (C_1-C_6)alkanoyloxy, (C_1-C_6)alkoxycarbonyl, NH_2, cyano, halo, hydroxy, nitro, carboxy, (C_3-C_8)cycloalkyl, (C_3-C_8)cycloalkoxy, trifluoromethoxy, or mercapto.

6. The compound of claim 5 wherein R_{20} is OH, methoxy, or propoxy; and R_{21} is H.

7. The compound of claim 5 wherein R_{20} and R_{21} together with the nitrogen to which they are attached form a pyrrolidin-1-yl, 1,3,4,9-tetrahydro-beta-carbolin-2-yl, piperidinyl, azetidinyl, 3,6-dihydro-2H-pyridin-1-yl, or 3,4-dihydro-1H-isoquinolin-2-yl ring, which ring is optionally substituted with $-C(=O)NH_2$.

8. The compound of claim 1 wherein R_9 has the following formula:

wherein:

R_{30} is $-C\equiv CR_{31}$, $-CH=CHR_{32}$, formyl, $-CH=NHNR_{33}$, $-CH=N(OR_{33})$, $-CH(OR_{34})$, or $-B(OR_{33})$;

R_{31} is tri(C_1-C_6)alkylsilyl, (C_1-C_6)alkoxy(C_1-C_6)alkyl, heteroaryl, aryl, Carboxy, or (C_1-C_6)alkoxycarbonyl;

R_{32} is hydrogen or *cis*-(C_1-C_6)alkoxy;

R_{33} is H or (C_1-C_6)alkyl; and

R_{34} is (C_1-C_6)alkyl;

wherein each aryl or heteroaryl of R_{31} is optionally substituted with one or more (C_1-C_6)alkyl, (C_1-C_6)alkylthio, (C_1-C_6)alkoxy, (C_1-C_6)alkanoyl, (C_1-C_6)alkanoyloxy, (C_1-C_6)alkoxycarbonyl, $NR_{35}R_{36}$, $-C(=O)NR_{35}R_{36}$, cyano, halo,

hydroxy, nitro, carboxy, (C_3-C_8)cycloalkyl, (C_3-C_8)cycloalkoxy, guanidino, trifluoromethoxy, mercapto, -S(=O)$_m$$R_{37}$, or trifluoromethyl;

m is 0, 1, or 2;

R_{35} and R_{36} are each independently H, (C_1-C_6)alkyl or (C_1-C_6)alkanoyl;

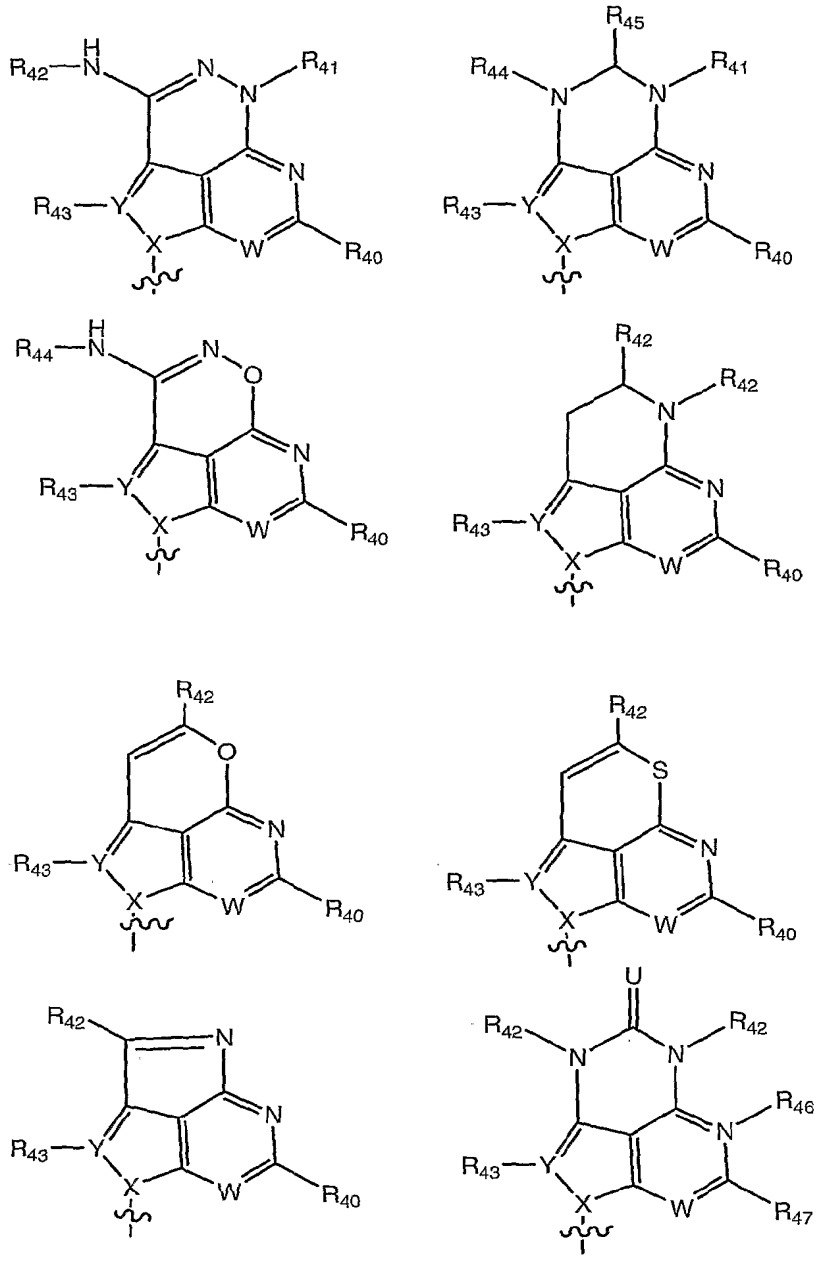
R_{37} is (C_1-C_6)alkyl, aryl, hetrocycle, or $NR_{38}R_{39}$; and

R_{38} and R_{39} are each independently H, (C_1-C_6)alkyl or (C_1-C_6)alkanoyl;

wherein each aryl or heterocycle of R_{37} is optionally substituted with one or more (C_1-C_6)alkyl, (C_1-C_6)alkylthio, (C_1-C_6)alkoxy, (C_1-C_6)alkanoyl, (C_1-C_6)alkanoyloxy, (C_1-C_6)alkoxycarbonyl, $NR_{35}R_{36}$, -C(=O)$NR_{35}R_{36}$, cyano, halo, hydroxy, nitro, carboxy, (C_3-C_8)cycloalkyl, (C_3-C_8)cycloalkoxy, guanidino, trifluoromethoxy, mercapto, or trifluoromethyl.

9. The compound of claim 8 wherein R_{30} is 2-trimethylsilylethynyl, 2-(2-pyridyl)ethynyl, 2-(4-pyridyl)ethynyl, 2-(4-methoxy)ethynyl, 2-(aminocarbonyl)ethynyl, 3,3-diethoxypropyn-1-yl, 2-(dimethylaminocarbonyl)ethynyl, 2-(N-amino(aminocarbonyl)ethynyl, 2-carboxyethynyl, 2-ethoxycarbonylethynyl, 2-methoxycarbonylethynyl, 2-phenylethynyl, 2-(4-fluorophenyl)ethynyl, 2-(4-methylphenyl)ethynyl, vinyl, 2-methoxyvinyl, formyl, -CH=N-NH_2, -CH=NOH, 1,1-diisopropoxymethyl, or -B(OH)$_2$.

10. The compound of claim 1 wherein R_9 has one of the the following formulae:



wherein:

R_{40} is H, $NR_{4a}R_{4b}$, $NHC(=O)R_{4b}$, $(C_1\text{-}C_6)$alkyl$NR_{4a}R_{4b}$, $NHNH_2$, cyano, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, aryl$(C_1\text{-}C_6)$alkyl, heterocycle$(C_1\text{-}C_6)$alkyl, halo, $(C_1\text{-}C_6)$alkylthio, $(C_1\text{-}C_6)$alkoxy, hydroxy, or mercapto;

R_{41} is H, (C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, heterocycle, aryl, or aryl(C_1-C_6)alkyl;

each R_{42} is independently H, hydroxy, mercapto, cyano, -$SNR_{4c}R_{4d}$, -$C(NH)NR_{4c}R_{4d}$, -C(=NH)NHOH, -$C(NH)NHO_{4c}$, -$C(=NH)NHNR_{4c}R_{4d}$, $NHCOR_{4c}$, SR_{4c}, OR_{4c}, SOR_{4c}, SO_2R_{4c}, -$C(=O)NR_{4c}R_{4d}$, -$C(=S)NR_{4c}R_{4d}$, or R_{4c};

R_{43} is H, hydroxy, $NR_{4c}R_{4d}$, $NHC(=O)NR_{4c}$, $NHNHR_{4c}$, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, heterocycle, aryl, aryl(C_1-C_6)alkyl, halo, $COOR_{4c}$, $CONR_{4c}R_{4d}$, or absent when Y is N;

R_{4a} and R_{4b} are each independently hydrogen, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, heterocycle, or aryl;

R_{4c}, and R_{4d} are each independently hydrogen, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, heterocycle, or aryl;

X, Y, and W are each independently N, C, CR_{4c}, S or P;

R_{44} is H, hydroxy, mercapto, cyano, -$SNR_{4c}R_{4d}$, -$C(NH)NR_{4c}R_{4d}$, -C(=NH)NHOH, -$C(NH)NHOR_{4c}$, -$C(=NH)NHNR_{4c}R_{4d}$, $NHCOR_{4c}$, SR_{4c}, OR_{4c}, SOR_{4c}, SO_2R_{4c}, -$C(=O)NR_{4c}R_{4d}$, -$C(=S)NR_{4c}R_{4d}$, or R_{4c};

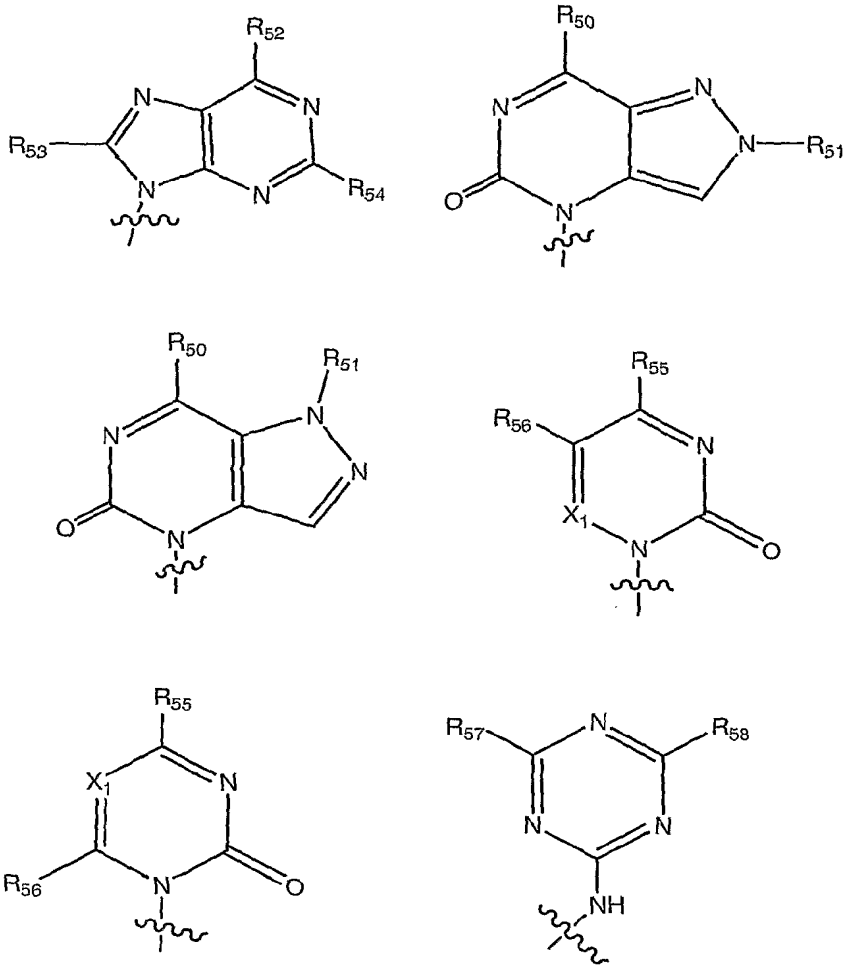
R_{45} is H, hydroxy, mercapto, cyano, -$SNR_{4c}R_{4d}$, -$C(NH)NR_{4c}R_{4d}$, -C(=NH)NHOH, -$C(NH)NHO_{4c}$, -$C(=NH)NHNR_{4c}R_{4d}$, $NHCOR_{4c}$, SR_{4c}, OR_{4c}, SOR_{4c}, SO_2R_{4c}, -$C(=O)NR_{4c}R_{4d}$, -$C(=S)NR_{4c}R_{4d}$, or R_{4c};

R_{46}, and R_{47} together with the atoms to which they are attached form a heterocyclic ring; and

U is S or O;

wherein each aryl or heterocycle is optionally substituted with one or more (C_1-C_6)alkyl, (C_1-C_6)alkylthio, (C_1-C_6)alkoxy, (C_1-C_6)alkanoyl, (C_1-C_6)alkanoyloxy, (C_1-C_6)alkoxycarbonyl, cyano, halo, hydroxy, nitro, carboxy, (C_3-C_8)cycloalkyl, (C_3-C_8)cycloalkoxy, trifluoromethoxy, mercapto, or trifluoromethyl.

11. The compound of claim 1 wherein R_9 has one of the following formulae:



wherein:

R_{50} is $NR_{5a}R_{5b}$, $ONR_{5a}R_{5b}$, $NR_{5a}NR_{5a}R_{5b}$, SR_{5b}, OR_{5b}, H, hydroxy, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkenyl, $(C_1$-$C_6)$alkynyl, or aryl;

R_{51} is $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkanoyl, or aryl;

R_{52} is $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkenyl, $(C_1$-$C_6)$alkynyl, or aryl;

R_{53} is H, halo, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkenyl, $(C_1$-$C_6)$alkynyl, or aryl;

R_{54} is H or NH_2;

R_{55} is $NR_{5a}R_{5b}$, $ONR_{5a}R_{5b}$, $NR_{5a}NR_{5a}R_{5b}$, SR_{5b}, OR_{5b}, H, hydroxy, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkenyl, $(C_1$-$C_6)$alkynyl, or aryl;

R_{56} is H, halo, $(C_1$-$C_6)$alkyl, or $(C_1$-$C_6)$alkenyl;

R_{57} and R_{58} are each independently –L-R_{5c};

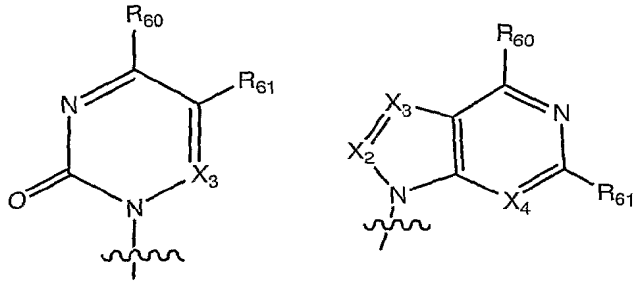
each L is independently a direct bond, -N(R_{5a})-, O or S;

each R_{5a} and R_{5b} is independently H, hydroxy, (C_1-C_6)alkyl, (C_1-C_6)alkenyl, (C_1-C_6)alkynyl, or aryl; and

each R_{5c} is $NR_{5a}R_{5b}$, H, hydroxy, (C_1-C_6)alkyl, (C_1-C_6)alkenyl, (C_1-C_6)alkynyl, or aryl;

wherein each (C_1-C_6)alkyl, (C_1-C_6)alkenyl, (C_1-C_6)alkynyl, or aryl of R_{50}-R_{58} and R_{5a}-R_{5c} is optionally substituted with one or more (C_1-C_6)alkyl, (C_1-C_6)alkylthio, (C_1-C_6)alkoxy, (C_1-C_6)alkanoyl, (C_1-C_6)alkanoyloxy, (C_1-C_6)alkoxycarbonyl, cyano, halo, hydroxy, nitro, carboxy, (C_3-C_8)cycloalkyl, (C_3-C_8)cycloalkoxy, trifluoromethoxy, mercapto, or trifluoromethyl.

12. The compound of claim 1 wherein R_9 has one of the the following formulae:



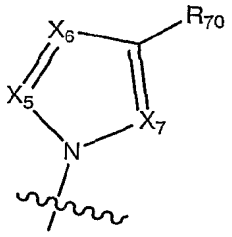
wherein:

X_2, X_3, and X_4 are each independently N, CH, or C-R_{6a};

R_{60}, R_{61}, and R_{6a} are each independently H, halo, $NR_{6b}R_{6c}$, hydroxyamino, $NR_{6b}NR_{6b}R_{6c}$, N_3, NO, NO_2, formyl, cyano, -C(=O)$NR_{6b}R_{6c}$, -C(=S)$NR_{6b}R_{6c}$, -C(=O)OR_{6b}, R_{6b}, OR_{6b}, or SR_{6b}; and

R_{6b}, and R_{6c} are each independently H, (C_1-C_6)alkyl, (C_1-C_6)alkenyl, (C_1-C_6)alkynyl, aryl, (C_1-C_6)alkanoyl, or aryl(C_1-C_6)alkyl.

13. The compound of claim 1 wherein R_9 has the following formula:



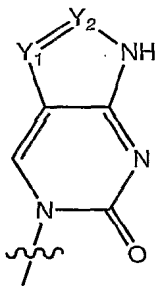
wherein:

X_5, X_6, and X_7 are each independently N, CH, or C-R_{7a};

R_{70} and R_{7a} are each independently H, halo, $NR_{7b}R_{7c}$, hydroxyamino, $NR_{7b}NR_{7b}R_{7c}$, N_3, NO, NO_2, formyl, cyano, -C(=O)$NR_{7b}R_{7c}$, -C(=S)$NR_{7b}R_{7c}$, -C(=O)OR_{7b}, R_{7b}, OR_{7b}, or SR_{7b}; and

R_{7b}, and R_{7c} are each independently H, (C_1-C_6)alkyl, (C_1-C_6)alkenyl, (C_1-C_6)alkynyl, aryl, (C_1-C_6)alkanoyl, or aryl(C_1-C_6)alkyl.

14. The compound of claim 1 wherein R_9 has the following formula:

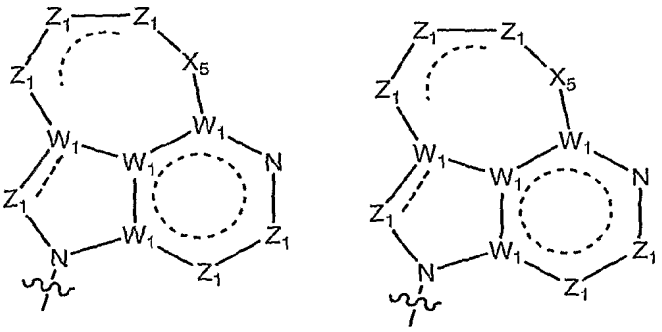


wherein:

Y_1=Y_2 is –N=N-, -CH=N-, -N=CR_{8a}-, or –CH=CR_{8a}-; and

each R_{8a} is independently H, halo, or (C_1-C_6)alkyl.

15. The compound of claim 1 wherein R_9 has one of the following formulae:



wherein:

each Z_1 is independently N, C-R_{9a}, O, S, NR_{9b}, >C=O, >C=S, >C=NR_{9b}, >S=O, $>S(O)_2$ or CH-R_{9a}; *provided that if a* Z_1 *participates in an optional bond* represented by a dotted line --- in the formula, then that Z_1 is N or C-R_{9a}; and *provided that if a* Z_1 *does not participate in an optional bond* represented by a dotted line --- in the formula, then that Z_1 is O, S, NR_{9b}, >C=O, >C=S, >C=NR_{9b}, >S=O, $>S(O)_2$ or CH-R_{9a};

X_5 is O, S, SO, SO_2; Se, SeO, SeO_2 or NR_{9b};

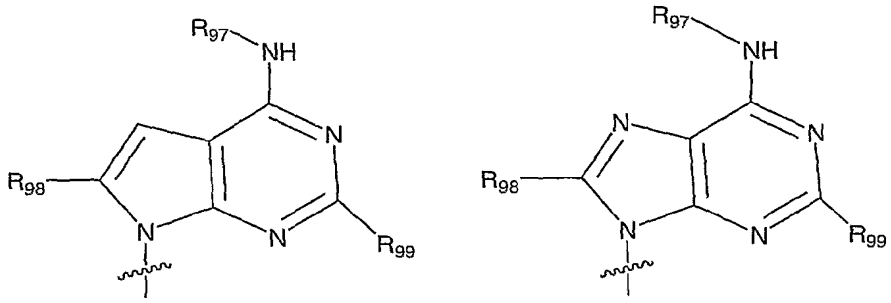
each W_1 is C, CH, or N; wherein if a W_1 participates in an optional bond represented by a dotted line --- in the formula, then that W_1 is C; and if a W_1 does not participate in an optional bond represented by a dotted line --- in the formula, then that W_1 is CH, or N;

each R_{9a} is independently H, halo, $NR_{9c}R_{9d}$, hydroxyamino, $NR_{9c}NR_{9c}R_{9d}$, N_3, cyano, -C(=O)$NR_{9c}R_{9d}$, -C(=S)$NR_{9c}R_{9d}$, -C(=S)$NR_{9c}R_{9d}$, -C(=NH)OR_{9c}, R_{9c}, OR_{9c}, or SR_{9c};

each R_{9b} is independently H, (C_1-C_6)alkyl, (C_1-C_6)alkenyl, (C_1-C_6)alkynyl, aryl, (C_1-C_6)alkanoyl, or aryl(C_1-C_6)alkyl; and

R_{9c}, and R_{9d} are each independently H, (C_1-C_6)alkyl, (C_1-C_6)alkenyl, (C_1-C_6)alkynyl, aryl, (C_1-C_6)alkanoyl, or aryl(C_1-C_6)alkyl.

16. The compound of claim 1 wherein R_9 has one of the following formulae:



wherein:

R_{97} is H, hydroxy, mercapto, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, $(C_2\text{-}C_6)$alkenyl, $(C_3\text{-}C_8)$cycloalkyl, aryl$(C_1\text{-}C_6)$alkyl, aryl or $(C_2\text{-}C_6)$alkynyl

R_{98} is H, hydroxy, mercapto, or $(C_1\text{-}C_6)$alkyl;

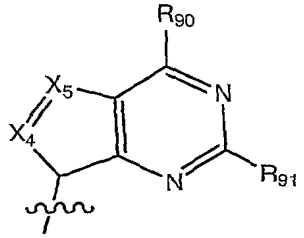
R_{99} is H, halo, azido, cyano, nitro, OR_{99a}, SR_{99a}, $NR_{99b}R_{99c}$, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_3\text{-}C_8)$cycloalkyl, aryl$(C_1\text{-}C_6)$alkyl, aryl or $(C_2\text{-}C_6)$alkynyl;

each R_{99a} is independently H, $(C_1\text{-}C_6)$alkyl, or $(C_1\text{-}C_6)$alkanoyl;

each R_{99b} and R_{99c} is independently H, $(C_1\text{-}C_6)$alkyl, or $(C_1\text{-}C_6)$alkanoyl;

wherein each $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy $(C_1\text{-}C_6)$alkenyl, $(C_1\text{-}C_6)$alkynyl, $(C_3\text{-}C_8)$cycloalkyl, aryl, and aryl$(C_1\text{-}C_6)$alkyl of R_{97}, R_{98}, R_{99}, R_{99a}, R_{99b}, and R_{99c}, is optionally substituted with one or more $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkylthio, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkanoyl, $(C_1\text{-}C_6)$alkanoyloxy, $(C_1\text{-}C_6)$alkoxycarbonyl, NH_2, cyano, halo, azido, hydroxy, nitro, carboxy, trifluoromethoxy, aryl, or mercapto.

17. The compound of claim 1 wherein R_9 has the following formula:



wherein:

X_4 is CR_{90a} or N;

X_5 is O, S, or NR_{91a};

R_{90} and R_{91} are each independently H, halo, hydroxy, $(C_1\text{-}C_6)$alkoxy, $NR_{90b}R_{91b}$, or heterocycle;

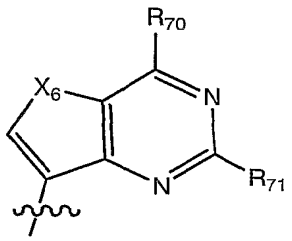
R_{90a} is H, halo, methyl, azido, or amino;

R_{91a} is H, or $(C_1\text{-}C_6)$alkyl; and

R_{90b} and R_{91b} are each independently H, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_8)$cycloalkyl, or aryl$(C_1\text{-}C_6)$alkyl;

wherein each $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_8)$cycloalkyl, aryl$(C_1\text{-}C_6)$alkyl, and heterocycle of R_{90}-R_{91}, R_{91a}, and R_{90b}-R_{91b} are optionally substituted with one or more (e.g. 1, 2, 3, or 4) halo, hydroxy, amino, $(C_1\text{-}C_6)$alkyl, and $(C_1\text{-}C_6)$alkoxy.

18 The compound of claim 1 wherein R_9 has the following formula:



wherein:

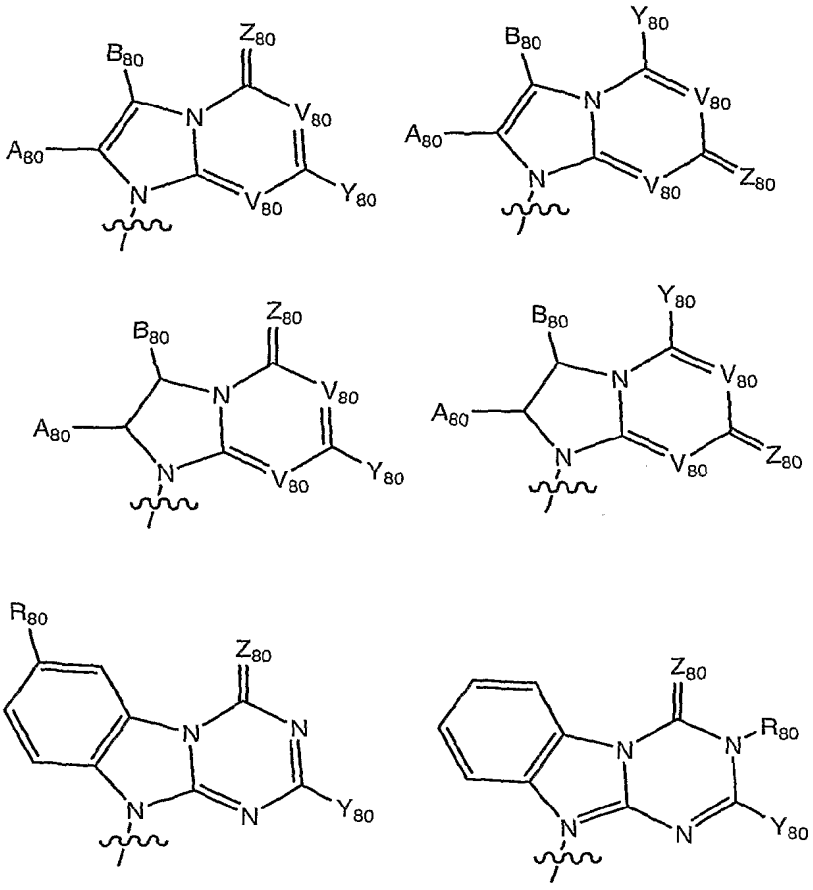
X_6 is O, S, or NR_{70a};

R_{70} and R_{71} are each independently H, halo, hydroxy, mercapto, aryl, heterocycle, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkenyl, $(C_1\text{-}C_6)$alkynyl, $(C_1\text{-}C_6)$alkylthio, arylthio, -S(=O)$(C_1\text{-}C_6)$alkyl, -S(=O)$_2(C_1\text{-}C_6)$alkyl, -S(=O)$_2NR_{70b}R_{71b}$, $NR_{70b}R_{71b}$, $(C_1\text{-}C_6)$alkoxy, aryloxy, (heterocycle)oxy;

R_{70a} is H, methyl, ethyl, or acetyl; and

R_{70b} and R_{71b} are each independently H, $(C_1\text{-}C_6)$alkyl, aryl, aryl$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkanoyl, or aryl-C(=O)-;

19. The compound of claim 1 wherein R_9 has one of the following formulae:



wherein:

A_{80}, B_{80}, and Y_{80}, are each independently H, halo, OR_{80}, $S(O)_nR_{80}$, $NR_{80}R_{81}$, cyano, trifluoromethyl, $C(=W)OR_{80}$, $C(=W)SR_{80}$, $C(=W)NR_{80}R_{81}$, nitro, azido, carbocyclic, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkenyl, $(C_1\text{-}C_6)$alkynyl, aryl, aryl$(C_1\text{-}C_6)$alkyl, or heterocycle; or A_{80} and B_{80} taken together with the carbon atoms to which they are attached from a 4-7 membered carbocyclic or heterocyclic ring;

n is 0, 1, or 2

Z_{80} is O, S, NR_{80}, or $CR_{80}R_{81}$;

each V is independently N or CR_{80}; and

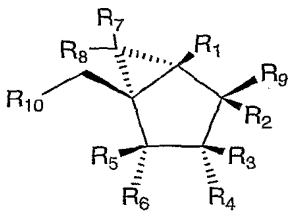
each R_{80} and R_{81} is independently H, carbocycle, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkenyl, $(C_1\text{-}C_6)$alkynyl, halo, $(C_1\text{-}C_6)$alkoxy, amino, methylamino, dimethylamino, cyano, $(C_1\text{-}C_6)$alkanoyl, aryl, aryl$(C_1\text{-}C_6)$alkyl, an amino acid

residue (e.g. a natural amino acid residue) or heterocycle; or R_{80} and R_{81} taken together with the atom(s) to which they are attached form a 3-7 membered carbocyclic or heterocyclic ring.

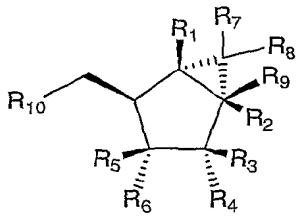
20. The compound of claim 1 wherein R_9 is adenine, guanine, cytosine, uracil, thymine, 7-deazaadenine, 7-deazaguanine, 7-deaza-8-azaguanine, 7-deaza-8-azaadenine, inosine, nebularine, nitropyrrole, nitroindole, 2-aminopurine, 2-amino-6-chloropurine, 2,6-diaminopurine, hypoxanthine, pseudouridine, pseudocytosine, pseudoisocytosine, 5-propynylcytosine, isocytosine, isoguanine, 7-deazaguanine, 2-thiopyrimidine, 6-thioguanine, 4-thiothymine, 4-thiouracil, O^6-methylguanine, N^6-methyladenine, O^4-methylthymine, 5,6-dihydrothymine, 5,6-dihydrouracil, 4-methylindole, substituted triazole, or pyrazolo[3,4-D]pyrimidine.

21. A prodrug of a compound of claim 1 werein R_{10} is OH, or $-OP(=O)(OH)_2$.

22. A pharmaceutical composition comprising a pharmaceutical excipient and a compound of formula I or II:



(I)



(II)

wherein:

R_1 is H, halo, OR_a, SR_a, or NR_bR_c;

R_2 is H, halo, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, or $(C_2\text{-}C_6)$alkynyl;

R_3 is H, halo, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, or $(C_2\text{-}C_6)$alkynyl; and R_4 is H, halo, azido, cyano, nitro, OR_a, SR_a, NR_bR_c, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, or

(C_2-C_6)alkynyl; or R_3 and R_4 taken together are =O, =NR_dR_e, =CR_fR_g; or R_3 and R_4 taken together with the carbon atom to which they are attached form a 3-7 membered carbocyclic ring wherein one carbon atom can optionally be replaced with -O-, -S-, or –NR_a-;

R_5 is H, halo, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, or (C_2-C_6)alkynyl; and R_6 is H, halo, azido, cyano, nitro, OR_a, SR_a, NR_bR_c, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, or (C_2-C_6)alkynyl; or R_5 and R_6 taken together are =O, =NR_dR_e, =CR_fR_g; or R_5 and R_6 taken together with the carbon atom to which they are attached form a 3-7 membered carbocyclic ring wherein one carbon atom can optionally be replaced with -O-, -S-, or –NR_a-;

R_7 and R_8 are each independently H or halo;

R_9 is a nucleoside base;

R_{10} is OH, -OP(=O)(OH)$_2$, -OP(=O)(OH)-P(=O)(OH)$_2$, -OP(=O)(OH)-P(=O)(OH)-P(=O)(OH)$_2$, or a phosphonate;

each R_a is independently H, (C_1-C_6)alkyl, or (C_1-C_6)alkanoyl;

each R_b and R_c is independently H, (C_1-C_6)alkyl, or (C_1-C_6)alkanoyl;

each R_d is independently H, (C_1-C_6)alkyl, or OH;

each R_e is independently H or (C_1-C_6)alkyl; and

each R_f and R_g is independently H, (C_1-C_6)alkyl, or halo;

wherein each (C_1-C_6)alkyl, (C_2-C_6)alkenyl, or (C_2-C_6)alkynyl of R_2-R_5 and R_a-R_g is optionally substituted with one or more halo, hydroxy, or (C_1-C_6)alkoxy;

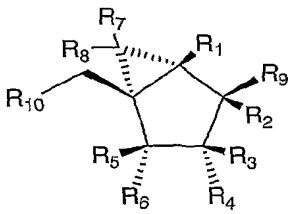
or a pharmaceutically acceptable salt or prodrug thereof;

provided the compound is not (1'*S*,2'*R*,3'*S*,4'*R*,5'*S*)-4-(6-amino-9H-purin-9-yl)-1-[phosphoryloxymethyl]bi-cyclo[3.1.0]hexane-2,3-diol; 5-(6-amino-9H-purin-9-yl)-1-[phosphoryloxymethyl]bicyclo[3.1.0]hexane-2,3-diol; 5-(6-amino-9H-purin-9-yl)-1-[hydoxymethyl]bicyclo[3.1.0]hexane-2,3-diol; (1'*S*,2'*R*,3'*S*,4'*R*,5'*S*)-4-(6-amino-9H-purin-9-yl)-1-[triphosphoryloxymethyl]bi-cyclo[3.1.0]hexane-2,3-diol; 5-(6-amino-9H-purin-9-yl)-1-[triphosphoryloxymethyl]bicyclo[3.1.0]hexane-2,3-diol; (1'*S*,2'*R*,3'*S*,4'*R*,5'*S*)-4-(2,4(*H*,3*H*)-dioxopyrimidin-1-yl)-1-(phosphoryloxymethyl)bi-cyclo[3.1.0]hexane-2,3-diol; (1'*S*,2'*R*,3'*S*,4'*R*,5'*S*)-4-(2,4(*H*,3*H*)-dioxopyrimidin-1-yl)-1- (diphosphoryloxymethyl)bicyclo[3.1.0]hexane-2,3-diol; or

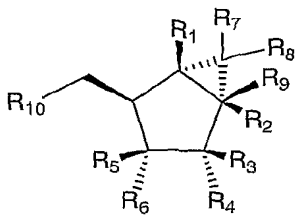
(1'*S*,2'*R*,3'*S*,4'*R*,5'*S*)-4-(2,4(H,3H)-dioxopyrimidin-1-yl)-1-(triphosphoryloxymethyl)bicyclo[3.1.0]hexane-2,3-diol.

23. A pharmaceutical composition comprising a pharmaceutical excipient and a compound, salt, or prodrug as described in any one of claims 1-22.

24. A method for treating a viral infection in an animal comprising administering to the animal an effective anti-viral amount of a compound of formula I or II:



(I)



(II)

wherein:

R_1 is H, halo, OR_a, SR_a, or NR_bR_c;

R_2 is H, halo, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, or $(C_2\text{-}C_6)$alkynyl;

R_3 is H, halo, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, or $(C_2\text{-}C_6)$alkynyl; and R_4 is H, halo, azido, cyano, nitro, OR_a, SR_a, NR_bR_c, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, or $(C_2\text{-}C_6)$alkynyl; or R_3 and R_4 taken together are =O, $=NR_dR_e$, $=CR_fR_g$; or R_3 and R_4 taken together with the carbon atom to which they are attached form a 3-7 membered carbocyclic ring wherein one carbon atom can optionally be replaced with -O-, -S-, or $-NR_a$-;

R_5 is H, halo, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, or $(C_2\text{-}C_6)$alkynyl; and R_6 is H, halo, azido, cyano, nitro, OR_a, SR_a, NR_bR_c, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, or $(C_2\text{-}C_6)$alkynyl; or R_5 and R_6 taken together are =O, $=NR_dR_e$, $=CR_fR_g$; or R_5 and R_6 taken together with the carbon atom to which they are attached form a 3-7 membered carbocyclic ring wherein one carbon atom can optionally be replaced with -O-, -S-, or $-NR_a$-;

R_7 and R_8 are each independently H or halo;

R_9 is a nucleoside base;

R_{10} is OH, -OP(=O)(OH)$_2$, -OP(=O)(OH)-P(=O)(OH)$_2$, -OP(=O)(OH)-P(=O)(OH)-P(=O)(OH)$_2$, or a phosphonate;

each R_a is independently H, (C_1-C_6)alkyl, or (C_1-C_6)alkanoyl;

each R_b and R_c is independently H, (C_1-C_6)alkyl, or (C_1-C_6)alkanoyl;

each R_d is independently H, (C_1-C_6)alkyl, or OH;

each R_e is independently H or (C_1-C_6)alkyl; and

each R_f and R_g is independently H, (C_1-C_6)alkyl, or halo;

wherein each (C_1-C_6)alkyl, (C_2-C_6)alkenyl, or (C_2-C_6)alkynyl of R_2-R_5 and R_a-R_g is optionally substituted with one or more halo, hydroxy, or (C_1-C_6)alkoxy;

or a pharmaceutically acceptable salt or prodrug thereof.

25. The method of claim 24 wherein the viral infection is Hepatitis C.

26. The use of a compound as described in any one of claims 1-22 in medical therapy.

27. The use of a compound as described in claim 26 to prepare a medicament useful for treating a viral infection in an animal.

28. The use of claim 27 wherein the viral infection is Hepatitis C.

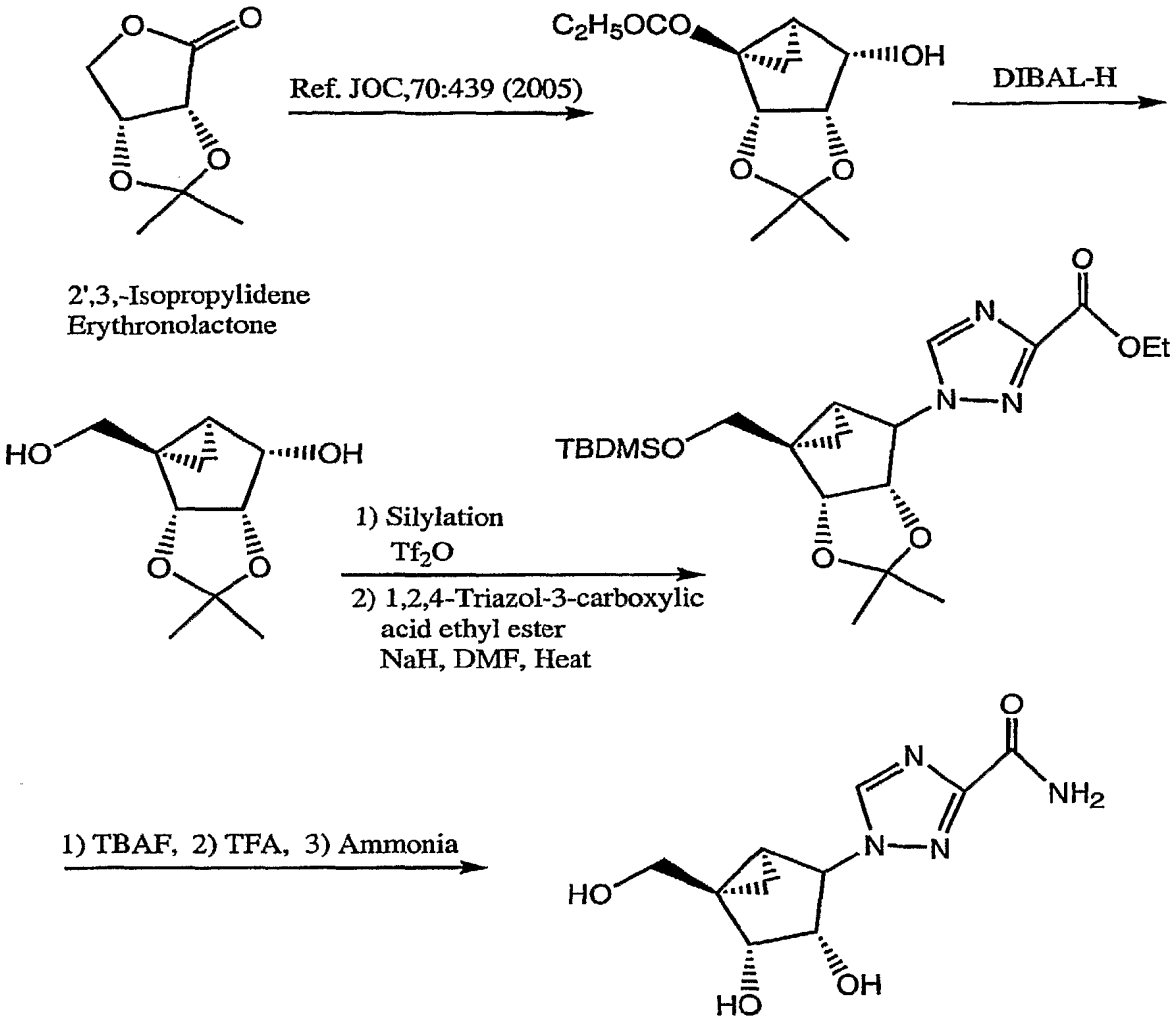

Ref. JOC,70:439 (2005)
DIBAL-H
2',3,-Isopropylidene
Erythronolactone
1) Silylation
Tf2O
2) 1,2,4-Triazol-3-carboxylic
acid ethyl ester
NaH, DMF, Heat
1) TBAF, 2) TFA, 3) Ammonia

Figure 1

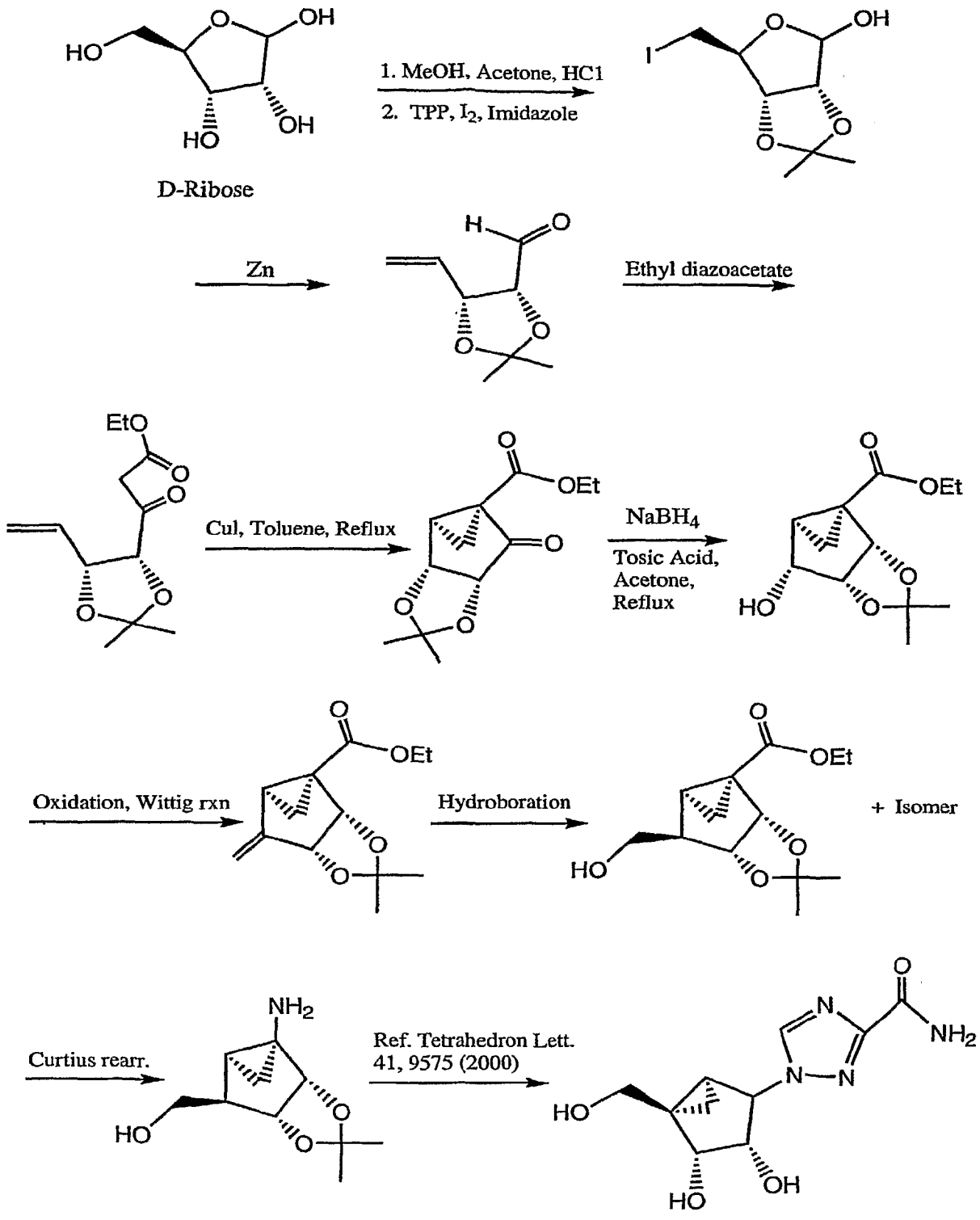

D-Ribose
1. MeOH, Acetone, HCl
2. TPP, I2, Imidazole
Zn
Ethyl diazoacetate
Cul, Toluene, Reflux
NaBH4
Tosic Acid,
Acetone,
Reflux
Oxidation, Wittig rxn
Hydroboration
+ Isomer
Curtius rearr.
Ref. Tetrahedron Lett.
41, 9575 (2000)

Figure 2

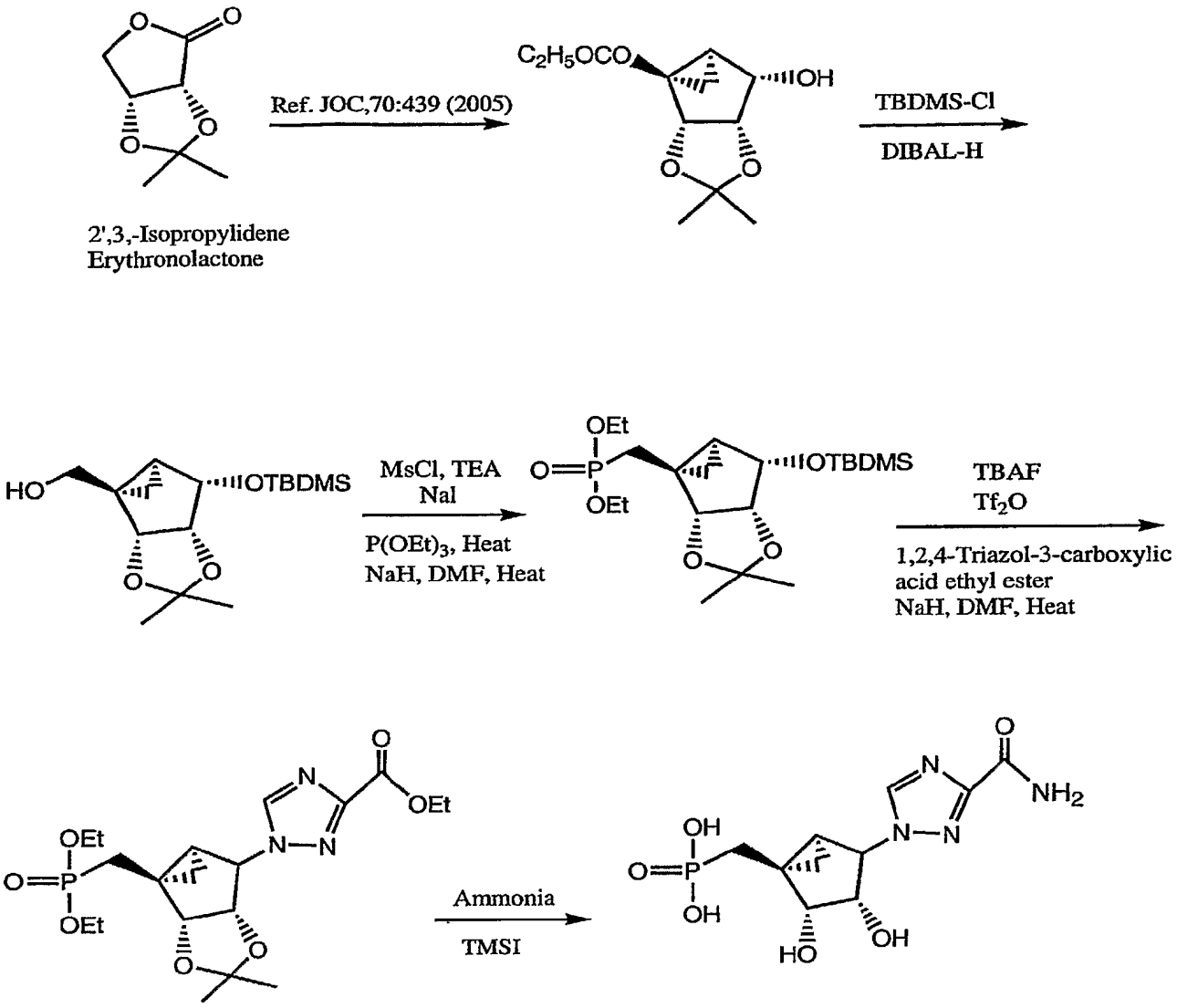
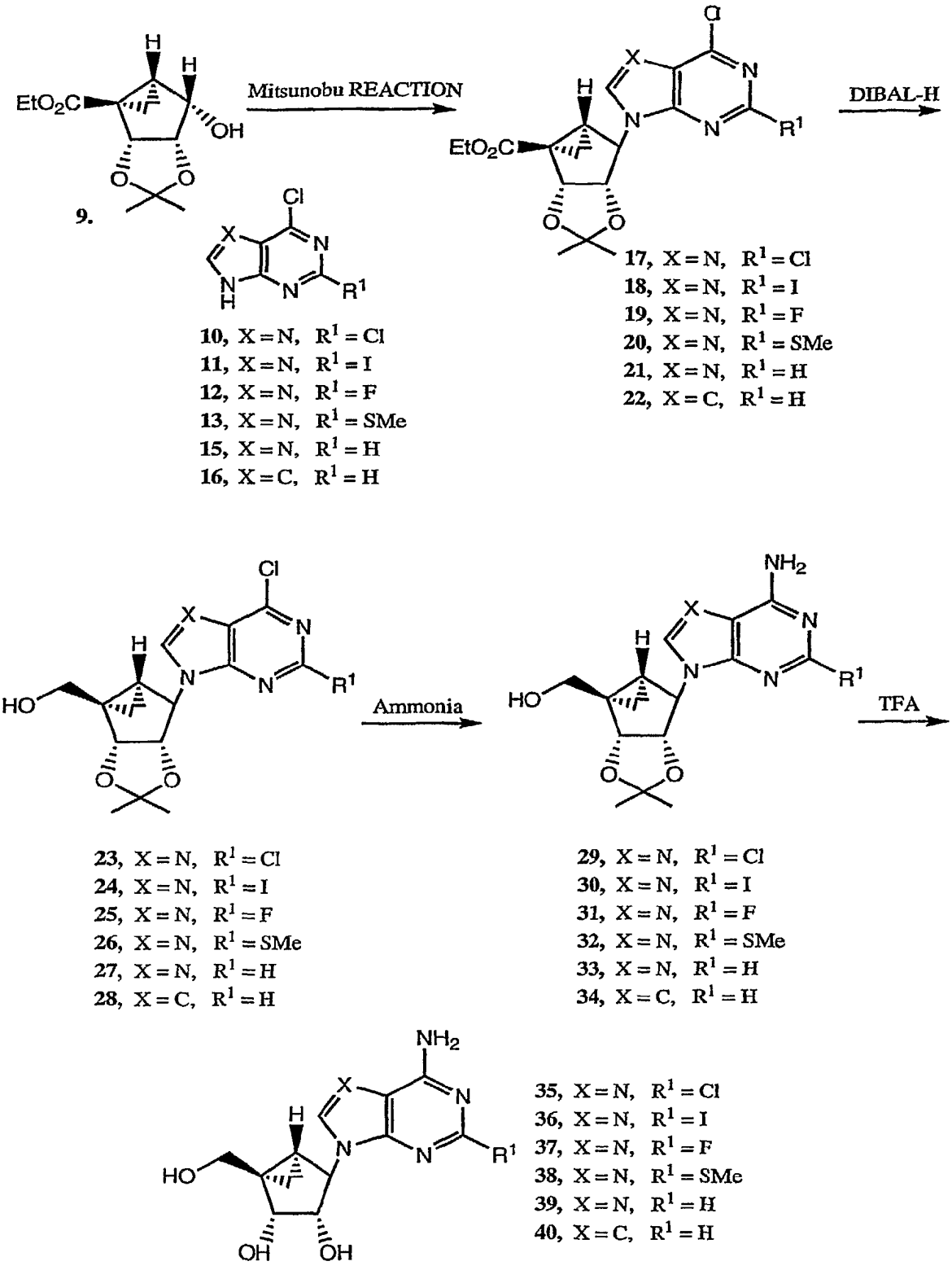

Ref. JOC,70:439 (2005)
TBDMS-Cl
DIBAL-H
2',3,-Isopropylidene
Erythronolactone
MsCl, TEA
NaI
P(OEt)3, Heat
NaH, DMF, Heat
TBAF
Tf2O
1,2,4-Triazol-3-carboxylic
acid ethyl ester
NaH, DMF, Heat
Ammonia
TMSI

Figure 3



9.

10, X = N, R^1 = Cl
11, X = N, R^1 = I
12, X = N, R^1 = F
13, X = N, R^1 = SMe
15, X = N, R^1 = H
16, X = C, R^1 = H

17, X = N, R^1 = Cl
18, X = N, R^1 = I
19, X = N, R^1 = F
20, X = N, R^1 = SMe
21, X = N, R^1 = H
22, X = C, R^1 = H

23, X = N, R^1 = Cl
24, X = N, R^1 = I
25, X = N, R^1 = F
26, X = N, R^1 = SMe
27, X = N, R^1 = H
28, X = C, R^1 = H

29, X = N, R^1 = Cl
30, X = N, R^1 = I
31, X = N, R^1 = F
32, X = N, R^1 = SMe
33, X = N, R^1 = H
34, X = C, R^1 = H

35, X = N, R^1 = Cl
36, X = N, R^1 = I
37, X = N, R^1 = F
38, X = N, R^1 = SMe
39, X = N, R^1 = H
40, X = C, R^1 = H

Figure 4

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/006763

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D473/40 A61K31/52 C07D473/36 C07D473/00 C07D487/04
A61K31/519 A61P31/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, EMBASE, BIOSIS, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 577 558 A (CIBA-GEIGY AG) 5 January 1994 (1994-01-05) Claims 1-67; Formula (I); examples	1-28
X	WO 02/08204 A (THE GOVERNMENT OF THE UNITED STATES OF AMERICA, AS REPRESENTED BY THE) 31 January 2002 (2002-01-31) Claims 1-20; Tables 1-3; compounds 2-5, 16-17	1-28
X	WO 98/05662 A (THE GOVERNMENT OF THE UNITED STATES OF AMERICA, RE) 12 February 1998 (1998-02-12) Claims 1-16; compounds 4, 20-22, 24-25; Tables 3-5	1-28

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 July 2006	26/07/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Kirsch, C

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95/08541 A (THE GOVERNMENT OF THE UNITED STATES OF AMERICA, RE) 30 March 1995 (1995-03-30) Claims 1-28; compounds 5-9, 31-32	1-28
X	US 5 869 666 A (MARQUEZ ET AL) 9 February 1999 (1999-02-09) Claims 1-16; compounds 5-9, 31-32	1-28
X	ALTMANN K-H ET AL: "4',6'-METHANO CARBOCYCLIC THYMIDINE: A CONFORMATIONALLY CONSTRAINEDBUILDING BLOCK FOR OILGONUCLEOTIDES" TETRAHEDRON LETTERS, ELSEVIER, AMSTERDAM, NL, vol. 35, no. 15, 1994, pages 2331-2334, XP000996351 ISSN: 0040-4039 Compound 5	1-28
X	MARQUEZ V E ET AL: "HIV-1 REVERSE TRANSCRIPTASE CAN DISCRIMINATE BETWEEN TWO CONFORMATIONALLY LOCKED CARBOCYCLIC AZT TRIPHOSPHATE ANALOGUES" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC, US, vol. 120, no. 12, 1998, pages 2780-2789, XP000996607 ISSN: 0002-7863 Compounds 1-2,6	1-28
X	EZZITOUNI A ET AL: "CONFORMATIONALLY LOCKED CARBOCYCLIC NUCLEOSIDES BUILT ON A BICYCLO3.1.0HEXANE TEMPLATE WITH A FIXED SOUTHERN CONFORMATION SYNTHESIS AND ANTIVIRAL ACTIVITY" JOURNAL OF THE CHEMICAL SOCIETY, PERKIN TRANSACTIONS 1, CHEMICAL SOCIETY. LETCHWORTH, GB, vol. 1, 1997, pages 1073-1078, XP000996608 ISSN: 0300-922X Compounds 1-10	1-28
X	RODRIGUEZ J B ET AL: "CONFORMATIONALLY LOCKED NUCLEOSIDE ANALOGUES. SYNTHESIS OF DIDEOXYCARBOCYCLIC NUCLEOSIDE ANALOGUES STRUCTURALLY RELATED TO NEPLANOCIN C" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 37, 1994, pages 3389-3399, XP000996507 ISSN: 0022-2623 Compounds 7, 9-13, 31	1-28

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SIDDIQUI M A ET AL: "SYNTHESIS, CONFORMATIONAL ANALYSIS, AND BIOLOGICAL ACTIVITY OF A RIGID CARBOCYCLIC ANALOGUE OF 2'-DEOXYARISTEROMYCIN BUILT ON A BICYCLOÚ3.1.0HEXANE TEMPLATE" NUCLEOSIDES & NUCLEOTIDES, MARCEL DEKKER, INC, US, vol. 15, no. 1/3, 1996, pages 235-250, XP000615548 ISSN: 0732-8311 Compounds 1-4	1-28
X	MARQUEZ V E ET AL: "CONFORMATIONALLY RESTRICTED NUCLEOSIDES. THE REACTION OF ADENOSINE DEAMINASE WITH SUBSTRATES BUILT ON A BICYCLO3.1.0HEXANE TEMPLATE" NUCLEOSIDES & NUCLEOTIDES, MARCEL DEKKER, INC, US, vol. 18, no. 4/5, 1999, pages 521-530, XP000996270 ISSN: 0732-8311 Compounds 1-5	1-28
X	MARQUEZ V E ET AL: "Nucleosides with a Twist. Can Fixed Forms of Sugar Ring Pucker Influence Biological Activity in Nucleosides and Oligonucleotides ?" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 39, 13 September 1996 (1996-09-13), pages 3739-3747, XP002094300 ISSN: 0022-2623 Compounds 1-5	1-28
X	RUSS PAMELA ET AL: "Synthesis and biological evaluation of 5-substituted derivatives of the potent antiherpes agent (north)-methanocarbathymine." JOURNAL OF MEDICINAL CHEMISTRY, vol. 46, no. 23, 6 November 2003 (2003-11-06), pages 5045-5054, XP002388422 ISSN: 0022-2623 Compounds 1a-1b, 2-4, 11, 14-15	1-28

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MARQUEZ VICTOR E ET AL: "Experimental and structural evidence that herpes 1 kinase and cellular DNA polymerase(s) discriminate on the basis of sugar pucker." JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 126, no. 2, 21 January 2004 (2004-01-21), pages 543-549, XP002388423 ISSN: 0002-7863 Compounds 1a-1b, 2a-2b	1-28
X	CHHATRIWALA MARIYA ET AL: "Induction of novel agonist selectivity for the ADP-activated P2Y1 receptor versus the ADP-activated P2Y12 and P2Y13 receptors by conformational constraint of an ADP analog" JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, vol. 311, no. 3, December 2004 (2004-12), pages 1038-1043, XP002388424 ISSN: 0022-3565 Compound MRS 2365	1-4,11, 12,16, 17, 19-24, 26,27
X	MAIER MARTIN A ET AL: "Synthesis and characterization of oligonucleotides containing conformationally constrained bicyclo(3.1.0)hexane pseudosugar analogs" NUCLEIC ACIDS RESEARCH, vol. 32, no. 12, July 2004 (2004-07), pages 3642-3650, XP002388425 ISSN: 0305-1048 Compounds 12-13	1-4,11, 12,16, 17, 19-24, 26,27
X	KIM HAK SUNG ET AL: "2-substitution of adenine nucleotide analogues containing a bicyclo(3.1.0)hexane ring system locked in a northern conformation: Enhanced potency as P2Y1 receptor antagonists." JOURNAL OF MEDICINAL CHEMISTRY, vol. 46, no. 23, 6 November 2003 (2003-11-06), pages 4974-4987, XP002388426 ISSN: 0022-2623 Compounds 22, 59	1-4,11, 12,16, 17, 19-24, 26,27
X	WALDO GARY L ET AL: "Quantitation of the P2Y1 receptor with a high affinity radiolabeled antagonist." MOLECULAR PHARMACOLOGY, vol. 62, no. 5, November 2002 (2002-11), pages 1249-1257, XP002388427 ISSN: 0026-895X Compound 4	1-4,11, 12,16, 17, 19-24, 26,27

-/--

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HERNANDEZ SUSANA ET AL: "Is the anomeric effect an important factor in the rate of adenosine deaminase catalyzed hydrolysis of purine nucleosides? A direct comparison of nucleoside analogues constructed on ribose and carbocyclic templates with equivalent heterocyclic bases selected to promote hydration" BIOORGANIC AND MEDICINAL CHEMISTRY, vol. 10, no. 8, August 2002 (2002-08), pages 2723-2730, XP002388428 ISSN: 0968-0896 Compounds 5-8, 11, 13, 19-21 -----	1-4,11, 12,16, 17, 19-24, 26,27
X	RAVI R GNANA ET AL: "Adenine nucleotide analogues locked in a Northern methanocarba conformation: Enhanced stability and potency as P2Y1 receptor agonists" JOURNAL OF MEDICINAL CHEMISTRY, vol. 45, no. 10, 9 May 2002 (2002-05-09), pages 2090-2100, XP002388429 ISSN: 0022-2623 Compounds 6a, 6c, 7a, 8a, 9a, 10a, 11a, 12a, 13a, 14a, 15a, 17a, 36-37, 42-45 -----	1-4,11, 12,16, 17, 19-24, 26,27
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	NANDANAN ERATHODIYIL ET AL: "Synthesis, biological activity, and molecular modeling of ribose-modified deoxyadenosine bisphosphate analogues as P2Y1 receptor ligands" JOURNAL OF MEDICINAL CHEMISTRY, vol. 43, no. 5, 9 March 2000 (2000-03-09), pages 829-842, XP002388445 ISSN: 0022-2623 Compounds 17a-17b, 23	1-4,11, 12,16, 17, 19-24, 26,27
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	WO 01/51490 A (THE GOVERNMENT OF THE UNITED STATES OF AMERICA, REPRESENTED BY THE SEC) 19 July 2001 (2001-07-19) Claims 1-22, 32-33; Formula 1, II-IV; compounds 4b-4c, 5c-9c, 12, 15-16, 17a-17b, 18-23; compounds of Table I	1-4,11, 12,16, 17, 19-24, 26,27
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X	RAVI G ET AL: "Synthesis and purine receptor affinity of 6-oxopurine nucleosides and nucleotides containing (N)-methanocarba-pseudoribose rings" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 11, 2001, pages 2295-2300, XP002362941 ISSN: 0960-894X Compounds 1, 5, 7a-7b, 8-10, 12, 20	1-4,11, 12,16, 17, 19-24, 26,27
X	TCHILIBON S ET AL: "(N)-Methanocarba 2,N6-disubstituted adenine nucleoside as highly potent and selective A3 adenosine receptor agonists" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 48, 23 September 2004 (2004-09-23), pages 1745-1758, XP002362942 ISSN: 0022-2623 Compounds 3-4	1-4,11, 12,16, 17, 19-24, 26,27

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	COSTANZI STEFANO ET AL: "Human P2Y(6) receptor: Molecular modeling leads to the rational design of a novel agonist based on a unique conformational preference" JOURNAL OF MEDICINAL CHEMISTRY, vol. 48, no. 26, December 2005 (2005-12), pages 8108-8111, XP002388449 ISSN: 0022-2623 Compounds 2, 4, 9-10 -----	1-4,11, 12,16, 17, 19-24, 26,27

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2006/006763

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 24-28 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2006/006763

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